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Mr. Colin Pollard
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A G E N D A

P R O C E E D I N G S

CHAIRMAN EGLINTON: Let's go ahead and come to order here.

Colin, it's not on the agenda; do we have to go through all of the initial housekeeping opening remarks, things like we did yesterday morning?

MR. POLLARD: No. All of those things, the conflict--the waivers, the temporary, that all applies today.

CHAIRMAN EGLINTON: All of that stuff is okay. They are allowed to have outbursts today?

[Laughter.]

MR. POLLARD: Well, you could remind them about a couple of the key aspects.

CHAIRMAN EGLINTON: They don't have to declare who is paying their way here today?

MR. POLLARD: It is probably worthwhile reminding everybody, when they come to the microphone, to identify themselves. I'm Colin Pollard with FDA.

CHAIRMAN EGLINTON: Thank you.

For anyone who was not here yesterday, please, when you wish to contribute, wait until you are acknowledged, come to the podium, and then identify yourself and your source of funding for your visit here today.

We have one leftover presentation from yesterday; Dr. Louis Burke, Medispectra.

DR. BURKE: Thank you very much. I apologize for not being here yesterday. The agenda reached me late, and it was impossible for me to change my own schedule. I appreciate the opportunity of allowing me to say a few words about this problem.

Where I come from is the Beth Israel Deaconess Medical Center in Boston, Massachusetts, and the Harvard Medical School.

I was interested in the use of the florescence of cervical cells, because after teaching for 25 years colposcopy and giving courses about colposcopy, I find that it has serious problems, which are getting worse, relative to the methods of compensation that we are facing in medicine; namely, managed care.

When one looks at various studies--and this is one done in Harlem by Hoppman. They had all of the references wrong. It's in Gynecologic Oncology of 1995--one looks at intraobserver and interobserver variability, and one can see that down at the either end of our spectrum of no disease too serious, intraepithelial neoplasia, whether it's cytology, histopathology, colposcopy, we all do pretty good. But when we are in the middle range of CIN I and CIN II and

now, today, HPV, we do rather poorly of both intraobserver and interobserver.

Now, this particular study had 23 colposcopists who studied 11 colpol photographs on two different occasions about two months apart. So that the intraobserver is the difference between these 23 colposcopists, and none of them would agree on any of the pictures of where the high-grade lesion was or where you should take the biopsy.

Now, this may not seem like a serious problem, but if managed care is going to tell us we can only do one or two biopsies, and the idea of splashing acetic acid onto the cervix and if it turns white, you take a bite out of it, we can't do that any more. I can't send down five, and six, and seven biopsies and hope that one of them is going to show me where the high-grade lesion is that maybe I'm not visualizing with my colposcope.

So that there are problems with colposcopy.

This is not only--just to point out that this problem is not only prevalent among colposcopists, it is prevalent among cytologists, and it's prevalent among pathologists, and this is a study of 100 cervical biopsy specimens that when one looks at the impression of the pathologists, one can see that when it comes to agreement of the high-grade lesion--invasive cancer, primarily--it is

very, very good.

When one looks at the CAP or anything above .7, it means that it is significant. Anything below .4 is very, very poor. And you see that down at the lower end of the spectrum they don't do very, very well. And, again, it is the same thing that we're having the problem in colposcopy. So we're looking for some other method, whereby we can help us determine what is the high-grade lesion.

Now, the other problem that I have deals with the common practice of using the electric excision of the transformation zone. It could be called "loop, LEEP, lepps" whatever you want to call it, but we have problems relative to this; namely, that maybe as high as 22 percent don't have any neoplasia when we do the procedure. Now, these are women who have had a biopsy that said it was high grade.

Now, my problem is that in Boston we are a referral center, and I have ladies coming from Provincetown, which is about 75 miles from Boston, or from Providence, which is 50 miles from Boston, and they get on the Southeast Expressway, which is one of the world's worst highways. It is similar to when you come from National Airport out here at around 5 o'clock in the afternoon.

And what we have are these women traveling to us to do a loop on them. And I've already had the biopsy or

they have been biopsied elsewhere and I've looked at the slide, and the biopsy says high-grade disease. And I put them on the table, and I look through the colposcope before doing it, and I don't see any disease.

Now, my problem is do I say, "Lady, I don't think you have any disease. You've got to go back another 50 miles or 75 miles through this traffic and then maybe we'll see you again in four months"? All because she is referred by a physician who is going to get angry that I did that, I go ahead and I do the loop. We all do.

And 22 percent don't show neoplasia or as high as 50 will have low-grade disease, which I don't usually treat. I don't believe low-grade disease should be treated. It's primarily a medical disease 80 percent of the time.

If the women will stop smoking, if they'll put their house in order as far as the number of sexual partners and clear up the STDs, it goes away in 18 months/2 years. You don't have to treat these ladies, and they're all young people. We're not talking about old people.

Now, wouldn't it be nice if this lady gets on the table, and I can do a test and say to her, "Look, I don't see anything, and I have confirmation on this test, which is so sensitive that you don't have disease, we're not going to do you."

And that means that we're going to save young people a procedure, which although has a great deal of safety, still carries with it certain implications relative to their getting pregnant and to their holding onto the pregnancy. So it is extremely important that we have an ancillary method that can help us with our problems with the loops.

So what we are looking for, therefore, is a method in which, first of all, we can direct our colposcopic biopsy to the proper site so we know that's going to be the worst lesion. That is my main use or I would hope be the main use of this particular technique, primarily to aid me so I don't have to do five biopsies to find the most proper site, but one biopsy or two biopsies.

We have already experienced with the various insurance companies that if I do five biopsies, they want all sorts of reports why they have to pay the pathologist for five biopsies; am I competent in doing colposcopy, what is my competence, why did I have to do five and not only one or two? They will pay for one and two, but they drag their heels when you are giving them more than the two biopsies. So that's a problem that is going to become more and more prevalent throughout the country.

I think the second problem, of course, is

evaluating the cervix, as I have said, prior to a loop procedure. And as far as triage between H- cell and L-cell, yeah, there are lots of things going on today about triaging these patients, and that is down on my third list of what I would want it for. There are other ways maybe we can triage our patients, possibly a little bit more efficiently than in this particular methodology.

So those are the few comments I would like to make of why we would like to use it, and then just a few comments about--First of all, some results that we have on a publication we are about to submit shows that this technique has high specificity and sensitivity to differentiate the presence of intraepithelial lesions and the absence of them and, more importantly, the difference between a high-grade lesion and a low-grade lesion or no-grade lesions at all.

I have not put figures up on there because we don't like to present data until it's in publication, and it's just being submitted. So these are the summaries of that particular paper.

Just a few comments about the suggestion about the clinical study design that was suggested to us.

First of all, the idea that the patient has to have a Pap smear only within the past four weeks is highly impractical. It should be extended to eight weeks. At

least the logistics of when a patient is told, especially patients who attend large clinics, they are told that they have an abnormal Pap smear and have to come for colposcopy, usually they rarely ever show up within four weeks. It is usually somewhere between eight and twelve weeks when we get to see them and especially during the summertime, where our clinic will run a--do not keep appointments as high as 30 percent while they go to the beaches rather than keeping their appointment for colposcopy. The idea of inclusion within four weeks is, I think, very impractical.

The study design. Patients where you exclude H-cell, except in the triage group, we think patients with H-cell should be included.

And as far as pregnant women are concerned, we are very, very apprehensive about including pregnant women, for a variety of reasons. We are not concerned about the effect of the methodology on the pregnancy or the cervix, but the fact that pregnant women, even when we are going to do a biopsy, and after 25 years we know I can biopsy cervices and not cause miscarriages or premature labor, you can't convince a pregnant patient of that, and she comes in very, very apprehensive, and is even concerned that you are going to put a speculum into her. So the idea of telling her I'm going to put a light on your cervix, and you can swear on a

stack of Bibles, she is not going to believe you. So that I don't think pregnant women, certainly at the start of all of this, should be included.

And just to reiterate what our intended use is; primarily is localizing the biopsy site and getting the area, which is really at risk, and determining from there how this patient should be treated.

Thank you very much for your attention.

CHAIRMAN EGLINTON: Thank you. And then we have Dr. Russ Lebovitz.

DR. LEBOVITZ: First I want to thank the panel and Dr. Harvey for giving me a few minutes to speak on one issue, and what I want to talk about is issues related to UV safety.

Let me identify myself. I am Russ Lebovitz. I am an M.D. pathologist. I have a Ph.D. in molecular biology. I have been involved for the past 15 years in basic research related to carcinogenesis and toxicity, and I am the author of more than 40 peer-reviewed papers in those fields. I have also completed training in business and financial management, and I am currently a partner in a Houston biotechnology consulting firm, Suma Partners, and I am serving in this capacity as an advisor and consultant to Life Spex in Kirkland, Washington, and my trip to FDA today

was paid for by Life Spex.

What I want to discuss in just a few minutes are four issues that were raised by both speakers yesterday and by the panel related to UV safety limits and standards.

And, in particular, the four issues I want to just briefly touch on are, first, the concept of biologically effective radiation in the UV region; the applicability of existing standards to tissues other than skin; the issue of whether the relationship between UV radiation and possible activation of viruses; and, fourth, the issue of operator safety as well as patient safety in UV devices.

I want to begin that in the draft document on page 4, and I just want to quote, are the proposed standards for UV radiation, and the quote that I would like to use is that "biologically effective radiation cannot exceed .003 jewels per centimeter squared between 180 and 400 nanometers."

I want to really start by discussing the concept of biologically effective radiation. It was touched on in some detail yesterday by Dr. Richards-Kortum, and I just want to re-emphasize the concept here.

So UV radiant dose I want to distinguish that from biologically effective radiation, where UV radiant dose is actually a physical measurement of the amount of UV energy falling on a given area.

In contrast, biologically effective radiation is really a normalized value. It's a calculated value rather than a directly measured value in which the UV radiant dose is adjusted to reflect the fact that high-energy UV-C--and we will talk about that in a second--is much more biologically potent than low-energy UV-A. But they are both measured in joule per centimeter squared. So there is some potential for confusion there.

Just to give some examples of comparing them. Using the proposed standard of 3 millijoules per centimeter squared of biologically effective radiation has very different consequences in different regions.

At 270 nanometers, the biologically effective radiation corresponding to 3 millijoules equals, actually, 3 millijoule radiant dose, where in the regions above 315, at least by the NIOSH and ACGIH standards, would be 1 joule per centimeter squared. That is at least a three hundredfold difference and, as Dr. Richards-Kortum referred to yesterday, that the actual biological action spectrum between UV-C around 260 or 270 and UV-A around 340 is probably much greater than 300. It may be as much as ten-thousandfold different.

But the standards, what I want to emphasize today, is that the proposed standards are very conservative in this

region. They are intended to protect people who have been exposed to UV radiation every day in the workplace. So they are very conservative.

And, again, the standard allows, if you look at the last line, biologically effective radiation, 3.5 minutes of sunlight through a glass window at sea level is really the amount of extra UV radiation that the standard allows and that the proposed standard for the Agency for these devices allows.

I think everyone here is exposed to at least that much every single day and without really any consequences. In fact, you need that much every day just to have normal Vitamin D metabolism.

Just briefly to review the electromagnetic spectrum with respect to UV.

You can see that on the left is both high energy and low wavelength, and as we move along the spectrum emphasizing the UV region, the ultraviolet radiation spectrum has been divided since approximately 1932 into three distinct regions, and these regions were really defined on the basis of very, very different biological effects.

The UV-C or germicidal UV was first identified because not only is it very toxic to human tissues, but also

to microbiological organisms. It is highly potent in terms of its biological effect. One joule has a much greater effect--a millionfold greater than something in the UV-A region. It induces mainly DNA damage directly. UV radiation in this region is absorbed by DNA. It leads to bond breakage and reformation, and there are significant risks from exposure to UV-C radiation, most notably cytotoxicity, carcinogenesis. But in light of the discussion yesterday by the panel, also it's very clear that certain viruses, and there is a great deal of work on Herpes Simplex and HIV can be activated by UV-C radiation.

UV-B is referred to as sunburn radiation because it's really the predominant high-energy UV that comes through the ozone. UV-C is completely excluded by the ozone. So UV-B is responsible for the sunburn and the erythema that we normally experience.

It's really, compared to UV-C, it's only moderately potent in terms of biological effects. It induces DNA direct damage, but with a relative potency of 1 percent or 1/1000th even of that of UV-C radiation, and there are still significant risks of cytotoxicity, carcinogenesis, and there have been a number of studies to show that UV-B radiation can also induce HIV and Herpes Simplex when they are latent and have integrated DNA. The

reason for that is that the activation of these viruses seems to require DNA damage in regions either directly involving the integrated viral DNA or in regions juxtaposed to that.

In contrast, UV-A, which is also referred to melanogenic or black light UV, is relatively weak. It is much weaker in terms of its biological effect. It induces DNA damage probably indirectly. It is probably not bound, it is not absorbed directly by the DNA, but rather through an indirect free radical mechanism. And the relative potency compared to UV radiation in the C-region is up to one million times less, and the risks are very limited. In particular, with respect to viral activation, a number of studies have been done with Herpes Simplex and with HIV, and there is no evidence, even at exposure levels of UV-A, that are significantly higher, at least one to two orders of magnitude higher than the proposed standards, there is no evidence, even at the PCR level, that there is activation of either Herpes Simplex or HIV.

And just, again, to reiterate the notion of the UV biological action spectrum, which was covered much more effectively yesterday by Dr. Richards-Kortum, just to remember that, if you see on the left, this is relative damage per joule at different wavelengths, and what you see

is, at least in terms of damage and biological potency, one joule does not equal one joule does not equal one joule, and that is the whole notion of having a concept of biologically effective radiation which normalizes all of these. So you are really comparing apples to apples rather than apples to oranges.

Now I want to just talk about the standard. The standard that has been proposed by the Agency for these devices is really originally developed by the National Institute of Occupational Safety and Health--NIOSH--and was first proposed in 1972 and has also been taken over, almost in its entirety, by ACGIH and ANSI.

And these are safety standards for UV exposure, and in these standards this is where the concept of biologically effective radiation was really first defined. These standards have been in place for greater than 25 years in work places all over the country, and they have been shown to be very safe and effective, and these are exposure limits that are being proposed for these devices, and they are also workplace exposures where individuals may be expected to have eight-hour-a-day exposure to these types of UV radiation and, yet, there is no evidence epidemiologically that there is any increased incidence of disease based on these exposures over a 25-year period.

This standard also specifically defines the coefficients used to calculate biologically effective radiation at different wavelengths, and most importantly, and this was not mentioned yesterday, these standards--and I have copies of them that I am going to give to Dr. Harvey--specifically mention that they are set for tissues that include the skin, but also mainly the eye and particularly the sensitive mucosa of the eye, and they are set to protect from photokeratosis.

The eye turns out to be one of the most UV-sensitive organs, and so I just want to reiterate that these are taken into account; that these standards are set to protect the eye under all circumstances.

Again, what NIOSH standards did was to set a safety limit that was below any measurable damage to the eye under any circumstances. And one of the things that is really important here, if you look, this really follows the NIOSH standard, and you will see that between 180 and 315 there is a curve. Well, that curve is defined on the basis of the biological action potential, and it really reflects the coefficients in the NIOSH standard.

If you will look at the bottom, the most sensitive region is really close to 270 or 280, and the reason for that is that that reflects the sensitivity of the eye to

photokeratosis. The actual sensitivity of DNA to radiation and of cytotoxicity in general is at about 254. So these standards are really set specifically for eye tissues and for the sensitive mucosa of the eye.

In conclusion, the NIOSH standards, which are also the ANSI standards, ACGIH standards, and the standards proposed by the Agency for these devices, clearly recognize the biological effects of UV light vary by at least three orders of magnitude between the UV-A and UV-C regions.

Second, the biologically effective radiation coefficients take into account very specifically and aggressively UV effects on the eye. The NIOSH standard for biologically effective radiation is very conservative and should be considered to be safe for both patients and operators.

Just a little bit more. The first point here is just, again, to reiterate, that in the biological action spectrum there are differences between UV-A and UV-C in damage caused that are a hundred thousandfold or greater; that studies indicate that pure UV-A radiation appears to pose no biological risk of measurable effects to doses at least of up to a thousand joules per centimeter squared, which is, again, three orders of magnitude higher than the standard that has been proposed here.

And then, finally, the very conservative nature of these standards has been demonstrated by studies showing that even in fair-skinned Caucasian individuals, that if they are exposed to pure UV-A that there is no measurable even erythema, which is a very low-dose injury, it does not occur until the standard has been exceeded by almost tenfold. So it is a very conservative standard.

Thanks.

CHAIRMAN EGLINTON: All right. Thank you very much.

We have Dr. Thomas Wright.

DR. WRIGHT: Good morning. I am Tom Wright. I am an associate professor of pathology at Columbia Presbyterian in New York, Columbia University. I am a gynecologic pathologist as well as a colposcopist. I also am a clinical advisor to Life Spex, Inc., which is developing in vivo diagnostic tests, and I am here today at the request of Life Spex to make some brief comments about the clinical applicability and about the document which is before you.

The draft guidance document is important because it sets a dialogue about developing an important new technology. By removing the uncertainty, which is inherent in both colposcopy and cytology, in vivo diagnostic technology could potentially improve the health care of many

women in the United States.

As the draft document illustrates, there are a number of unmet clinical needs in the United States surrounding Gyn cytology and colposcopy.

The in vivo diagnostic tests could be used as an adjunctive test for screening, together with a Pap smear. It could be used a way of managing women with low-grade cytologic abnormalities. This includes ASCUS and LSIL, both. And it could also be used as an aid to colposcopic evaluation of women at the time in which colposcopy is being performed, so in order to be a biopsy director.

As Mark Schiffman showed you yesterday, there is a large problem in the United States with respect to atypical Pap smears. This is frequently referred to as an atypical Pap smear pyramid. It is similar to what Dr. Schiffman showed you. The numbers are a little different, but they are quite similar.

There are about 50 million to 60 million Pap smears taken yearly in the United States. Of those, about 2.5 million are read out as being atypical squamous cells of undetermined significance. There are an additional 1 million smears yearly in this country read out as low-grade squamous intraepithelial lesions. 250,000 patients have high-grade SIL, and there are about 13- to 17 thousand

invasive cancers diagnosed, depending on which year you are looking at.

Clearly, the pyramid shape of this graph indicates that the problems lie mainly in the ASCUS and the LoSIL range, clinically. The clinicians are faced with large numbers of patients with these low-grade abnormal smears. High-grade disease and invasive cancer, luckily, are uncommon in this country.

The ASCUS Pap smear problem is clearly significant. There are a large number of cases in this country, and there is a lot of disagreement as to how to manage these patients. Some clinicians perform repeat Pap smears. They feel that they are comfortable and they are safe simply repeating the Pap smear as a way of managing these patients.

Other clinicians, however, are uncomfortable about following patients with repeat Pap smears and perform colposcopy on all patients with low-grade abnormal smears.

The problem of low-grade abnormal smears consumes a large amount of women's health care resources in this country and it also causes significant anxiety to the women who are diagnosed as having these smears. Women know that their smears are abnormal, and they are quite concerned about it.

This shows you the reasons that women are concerned about a low-grade abnormal Pap smear--an ASCUS smear. These are the rates of biopsy-confirmed high-grade disease, high-grade CIN, that is CIN 2 and 3, and low-grade disease among different groups of women which I have access to data on who were diagnosed as having an ASCUS.

Cytodiagnostics is a large national laboratory in New York State. They run an ASCUS rate of 2 percent. That means that 2 percent of all of their Pap smears are diagnosed as ASCUS at this particular laboratory.

Of the women who undergo colposcopy and evaluation, 38 percent of the women with ASCUS are found to have low-grade CIN on biopsy, and 13 percent have high-grade cervical cancer precursor lesions.

13 percent means one out of ten women with an ASCUS smear has a significant precancerous condition. When we look at women referred to our colposcopy clinic, we don't know what the overall rate is in those patients because they are referrals, but 25 percent of the women we see in colposcopy clinic have got biopsy-confirmed low-grade disease. 6 percent have high-grade disease.

And it varies from population to population. If we look at HIV-infected women in New York City, we find, again, 26 percent of those who have ASCUS smears will have

low-grade disease and 12 percent will have high-grade. So there is a significant burden of significant disease in women with ASCUS smears.

Currently, there are disadvantages to any of the ways in which we have for managing these patients. Cytology misses high-grade lesions. Simply repeating a Pap smear is not safe many women feel and many clinicians feel. They want some additional follow-up, some additional evaluation.

Colposcopy alone, though, is considered expensive. Many women do not want it. It is considered uncomfortable by women. They have had friends who have had colposcopy. They have been told how much biopsies hurt, and they don't want colposcopy performed.

In addition, and one of the more important points, is that colposcopy requires a high level of clinical expertise. As Dr. Burke just told you, it is not an easy science to teach clinicians. It takes many years of experience to be good at it, and even among clinicians who perform colposcopy on a daily basis, it is a highly subjective skill.

What we need for managing patients with low-grade cytologic abnormalities are objective measures of evaluating their disease rather than the subjective ones.

The second place where I think <u>in</u> <u>vivo</u> diagnostic

tests have the potential for having a dramatic impact on the management of women in this country is in managing patients who have biopsy-confirmed low-grade disease, not an atypical Pap smear, but biopsy-confirmed low-grade disease.

Many of these lesions occur in young patients and, again, like with the ASCUS smear problem, there is a controversy in this country as to how we manage these. Some of these patients are simply followed. Their clinicians feel comfortable that they have little risk for developing invasive cancer and, therefore, they follow them because many of the lesions go away.

However, other clinicians, such as at Columbia, we routinely treat patients with low-grade disease. It is a standard policy in our clinic to offer treatment to all of these women. And the reason I think that there are discrepancies between the management protocols is that the histologic appearance clearly does not predict the biologic behavior of these histologically low-grade lesions.

This is just one small table. It is from a review article published in the International Journal of Gynecologic Pathology, which tried to tie together the voluminous literature on the natural history of low-grade disease.

I just want to point out, when you look at the

women with mild dysplasia, CIN 1 or low-grade CIN, there have been 17 studies, and although two-thirds of the patients have spontaneous regression of their lesions if untreated, 22 percent of the women have persistent low-grade disease, and 16 percent of the women go on and progress to a higher grade lesion. So there is a large biological heterogeneity and, unfortunately, when we see an individual patient with low-grade disease, we do not know if she is going to be one of the two-thirds that spontaneously regresses or if she is going to be one of the 16 percent who has progressive disease.

The other problem which we see in the management of patients with low-grade disease and part of the reason whereby histopathology is probably not predictive of the biology or the outcomes in these patients is that the subjective nature of colposcopy makes it difficult to be certain that a patient who is diagnosed with having low-grade disease actually has low-grade disease.

Dr. Burke showed you a slide which looked at the KAPPA, the interobserver and intraobserver variation, for pathologists reading individual biopsies. But there is also a lot of sampling error which occurs when you perform colposcopy. The cervix is a relatively large surface area, and the colposcopist is supposed to look at the cervix,

determine which is the highest grade lesion on the cervix, and take one or two biopsies.

Because colposcopy is subjective frequently we get misrepresentation of disease status based on the actual process of colposcopy, and this is a study design which shows you that problem.

In this study--Bonardi published this one, although there are a number in the literature currently--what has been done is patients have undergone colposcopy and had a colposcopically directed biopsy taken, a so-called punch biopsy, and a diagnosis was made. It was either within normal limits, CIN 1, 2, or 3.

After having had that biopsy taken, the patients then underwent loop electrosurgical excision, where a wire loop is used to remove the entire transformation zone and then all of the transformation zone is observed histopathologically.

And when you look at the patients with CIN 1 in this study, there were 40 patients who had punch biopsies read out as CIN 1. But when you look at the results of their loop specimens, half of those patients had no disease on the loop specimen. Ten of them had--one out of four--had CIN 1, and an additional nine had high-grade disease rather than low-grade disease.

Clearly, we need different, more objective measures for determining the presence or absence of high-grade disease and the presence or absence of disease in women.

So in conclusion, I feel that there are clear, unmet clinical needs in the United States today with respect to the management of low-grade cytologic and cervical cancer precursor lesions. These unmet needs directly involve the lives of millions of women each year in this country.

What we need are objective methods for identifying and localizing both low-grade and high-grade precancerous conditions, and it's important that not only do we focus on the high-grade lesions because we know those are true cancer precursors, but we also need to focus on the ability of these tests to diagnose low-grade lesions. Remember, 12 percent to 15 percent of low-grade lesions have the capacity to progress. We may not want to treat them today, but certainly they are risk factors for the development of subsequent invasive cervical disease.

And, finally, because in vivo diagnostic testing has a potential for answering this large unmet clinical need, I think it's important that appropriate standards be developed, which you all are doing today, which will allow us to bring this new technology forward.

Thank you very much for your time.

CHAIRMAN EGLINTON: Thank you.

We are blessed to be just a little bit ahead of schedule here. Do any members of the panel have any questions for the last three presenters? Does anyone want to ask a question?

DR. SOLOMON: Tom, in your presentation, the transparency just before the last one where you showed the discrepancy between the biopsy versus the subsequent LEEP, it seemed to me that most of the off-diagonals may have been due to the fact that at biopsy it was a small lesion. You biopsied it and then at LEEP there simply was no residual lesion.

DR. WRIGHT: This is clearly a problem--

CHAIRMAN EGLINTON: You have to come to the microphone.

DR. HARVEY: You should speak at the mike.

DR. WRIGHT: I agree with you. This is a problem certainly with respect to small lesions. In the United States today, the majority of cases that we deal with are incident rather than prevalent precancerous conditions. So they tend to be relatively small.

So if a patient comes in and is evaluated with colposcopy, we take a biopsy, and a biopsy by itself can

remove the entire lesion. And frequently we are asked by clinicians to review the original biopsies, and often we will see that there was disease there. So that accounts for the underdiagnoses on the LEEP specimens.

To me, the more significant problem is actually the overdiagnoses because the patient has already been treated if they are "underdiagnosed on the LEEP." Because you do the loop excision, and they have been treated.

The real problem is, if you are in an institution or in a managed health care plan where you are only allowed to follow patients with low-grade disease and we find that one out of four patients with "low-grade disease" actually have high-grade disease, and we follow that patient and they are lost to follow-up, which frequently happens, that is where I feel the real clinical problem is.

CHAIRMAN EGLINTON: Dr. Schiffman?

DR. SCHIFFMAN: The Oster article has a very wide range, so that summary you show where it looks like here is an entity has bothered me. Because if you look in the tables it goes all of the way from minimal disease, where there is minimal risk, to persistent histologically confirmed yet untreated CIN 1, which approaches more of what Ralph is following in the 60s, CIN 1, were there seems like an almost inexorable sense of progression.

So one of my concerns has been that this diagnosis is so broad that whenever anybody mentions it you need a whole list of methodologic caveats to understand what has just been said. So it is very possible that some CIN 1 is truly CIN 3 at the time that the first biopsy--we are talking about the screen or the test versus the reality, the parameter, and I still think a lot of that is from misclassification of the low-grade rather than progressive potential.

DR. WRIGHT: The histopathologic diagnosis of low-grade CIN I agree totally, Mark, is a real problem. It has been a problem for 20 years, and it will continue to be a problem. Obviously, we need objective methods for determining the biological potential of a lesion. It's obviously not histopathology. There are a number of different approaches that can be taken for it.

We have looked at clinality, as you know, and when you look at clinality, you find that certain of these lesions are monoclonal, certain of the histologically low-grade lesions are polyclonal.

The monoclonal ones are the ones you would assume are going to be neoplastic as opposed to the polyclonal ones. I don't think we can tell histopathologically, which is why there is such a large range of outcomes.

DR. SCHIFFMAN: What I was trying to say, though, is a colposcopically directed biopsy suggesting CIN 1 or showing CIN 1 in a way is still a screen for the underlying reality of what the entire tissue shows.

DR. WRIGHT: I agree totally.

DR. SCHIFFMAN: And has that element of test rather than truth is what I was--

DR. WRIGHT: I agree, and that's why I think we need objective methods.

DR. O'LEARY: I think that Mark is into an interesting set of problems. You have three complicating things going on here and, quite frankly, I think it's probably beyond anybody to sort them out.

First, we have a disease that is dynamic and the dynamics is perhaps manifesting itself between the Pap smear and the biopsy, between the biopsy and the LEEP.

We have the dynamics with an interplay of sampling variation, not only sampling differences between the cytology and the biopsy, but, in fact, within a biopsy even what section one might be looking at. When we take a LEEP biopsy, we are only look at, perhaps, what, a millionth of the total amount once it gets under the microscope.

And then you are complicating that with the problem of intra- and interobserver variation, which is

certainly playing a part in some of this so-called regression and progression. How one sorts that out and finds the appropriate brass standard--because it is pretty clear we are not going to be doing natural history studies here--but the appropriate brass standard on which to evaluate a new technology, whether it be for rescreening Pap smears, as was dealt with by the FDA in the last couple of years, or this kind of technology--really an interesting set of problems. And I have got to admit it has me scratching my head.

CHAIRMAN EGLINTON: Dr. Davey?

DR. DAVEY: Just a couple more sort of related comments.

When you look at some CAP data, which I have been involved with, if you send out Pap smears that have been referenced as either low-grade or high-grade, it's about a 15 percent disagreement by participants on whether we call them low-grade and they're called high-grade. So that happens year after year.

And then, also, biopsy follow-up after a Pap, it's similar; about 15 percent of the time, when you have a low-grade lesion on Pap, it turns out to be high-grade on just--this could be either a LEEP or other kind of punch biopsy--so you get all of that over and over again. But it

seems to me that we are going to have to consider additional specimens because one of the things that could happen is the initial biopsies done on the patient, if we are going to use that as a standard, may show nothing, but yet a later specimen--a LEEP or something else--would show something else.

So we are going to have to figure out how to consider that data.

And, also, I would just sort of like to ask Dr. Schiffman what value there would be in collecting HPV data on some of these. I don't know that we can ask manufacturers to do it on all, but it seems to me if we start using HPV testing more, a few years from now, especially when the results of this trial come out, that if we don't include some of that as a recommendation we may be behind before you can get started evaluating these instruments.

DR. SCHIFFMAN: That is really a big topic, and I don't know whether we would want to take it on. I mean, it is a nonspecific--

DR. DAVEY: Right.

DR. SCHIFFMAN: --at the PCR level you find a high percentage of lesions that have no HPV.

DR. HARVEY: Would you talk into the mike, please.

DR. SCHIFFMAN: I'm sorry. I thought I was.

If a large percentage of a group of lesions is HPV negative, I have intended to call it not associated with cervical cancer pathway. However, there is a valid issue of exfoliation in that most of the HPV techniques right now are based on exfoliated scrapes or lavage. So if a lesion is not exfoliated for cytology, there would be correlated errors with it not exfoliating for HPV. HPV is more sensitive at the PCR level, so you may catch it on that and miss it on cytology. But I am leery without more evidence to talk about comparing biopsy punch issues with exfoliated issues because now you are talking about anatomic differences. In situ HPV techniques are insensitive and not very good. So it is a very complicated topic.

I think in any given protocol we can talk about it, but I have trouble talking about it, generally.

CHAIRMAN EGLINTON: Are there other questions?

[No response.]

CHAIRMAN EGLINTON: Colin, do you want to present the FDA questions and then we will take a break.

MR. POLLARD: Good morning, ladies and gentlemen of the panel.

FDA has prepared a draft guidance document for the preparation of an Investigational Device application--an

IDE--for in vivo devices for detection of cervical cancer and its precursors.

In particular, this document, which all of you have had a chance to go through, was developed to address a new class of optical detection devices that provide instantaneous readings when applied to the cervix. This guidance document addresses both feasibility studies and the pivotal safety and effectiveness studies that would support a PMA.

Please address the following questions about key aspects of the guidance document.

The first two questions are related to safety.

Question No. 1. As presently designed, these investigational devices expose the cervical tissue to one or more of the following energy sources: Optical radiation; that is, ultraviolet, visible or infrared, and low voltage electrical pulses.

Optical radiation may be produced by high-intensity broadband light sources; for example, xenon lamp, light-emitting diodes, or lasers.

Although published standards--ANSI and ACGIH--exist for determining occupational safe exposures to human skin, there is much less information on mucosal skin exposure. FDA proposes that manufacturers with devices

approaching the current skin limits conduct additional safety testing. And that is given on page 4 of the guidance document. You, obviously, have heard some other comments about that.

What kind of issue effects should FDA be concerned about for optical/electrical devices used as in vivo detection systems for cervical cancer? And some examples might be mutagenesis, carcinogenesis, viral activation, immunosuppression. And what study models are appropriate for testing these kinds of effects?

Question No. 2. Besides phototoxicity, material toxicity, electrical shock, and laceration/bleeding referenced in the draft guidance document, are there any other possible adverse effects that might result from the use of these in vivo devices?

There are three questions related to the effectiveness of this type of device.

Question 3. Several different indications for use have been proposed for this new detection technology, including primary and secondary screening, triage, et cetera. See page 8 of the guidance document.

Given these different possible indications:

Question 3a. What are appropriate study subject inclusion/exclusion criteria?

3b. What is the appropriate reference diagnosis for comparison? I think this is a very important question, and we have referred to a number of times yesterday and today already.

Question 3c. What is the appropriate sequence of testing the subject with different detection/diagnostic methods; for example, Pap smear, the new optical device, colposcopy, biopsy? Is blinding important? See the Sample Clinical Study Design of guidance document on pages 10 to 13.

There is a subquestion there: How does the study phase--the feasibility studies versus the pivotal efficacy study--affect these study design factors?

Question 4. These new types of in vivo devices may offer additional benefits to the patient compared with traditional Pap smear for detection of cervical cancer and its precursors; for example, noninvasive, instantaneous. To what extent do these factors influence the evaluation of the effectiveness, especially sensitivity, specificity, positive and negative predictive values, of in vivo compared to current alternatives? Does this differ for different populations or different indications for use?

And, finally, Question 5. Does the panel have any other recommendations for the draft guidance document?

Those are the discussion questions we put before the panel. We hope that that assists the panel as they go through the guidance document. We also would comment, although there has been panel input on the development of these questions, that the panel should not feel confined to these questions if they identify other key points for discussion.

CHAIRMAN EGLINTON: All right. Thank you. Let's take a break here now and resume at 9:40.

[Recess taken from 9:26 a.m. to 9:48 a.m.]

CHAIRMAN EGLINTON: Thank you. We have an added treat here mid-morning, a nonscheduled agenda item here. From the FDA's Office of Science Technology, Dr. Yonish Biers will help us understand a little bit more about radiation.

Dr. Biers?

DR. BIERS: Thank you.

I am Yonish Biers. I am with the Office of Science and Technology in CDRH. I am a researcher and I have been involved in studies on UV-induced and X-ray induced mutations, UV-induced carcinogenesis, and most recently I am involved in work on activation of HIV and the possible effects of UV on progression of HIV disease.

I would like to make some comments regarding the

use of ACGIH document for evaluation of the safety.

No. 1, I wanted to say that the document is pretty old, and it is, obviously, the coin has two sides. That means the document has been checked in time, but at the same time it does not incorporate the most recent advances in photobiology and photomedicine.

There are a number of new developments. I would like to illustrate some of them with two slides from our work. The first of these slides will show you results of our analysis regarding the effects of different wavelengths of UV radiation and activation of HIV promoter.

And you will see what was mentioned before by Dr. Lebovitz that the effects depend very strongly on wavelengths. They are very strong in the UV-B region, and they are weaker in the UV-A region. Yes, that is our action spectrum.

You can see wavelengths on the abscissa. You can see relative effectiveness on ordinate, and you can see that HIV promoter activating ability of UV drops dramatically, goes down to very low values, as we approach UV-A region.

Does that mean that UV-A is innocuous? In this particular case, yes, that is the case. We went to verify exposures of UV-A, and we don't get any activation.

But at the same time just last week we attended a

meeting of the American Society for Photobiology and we learned there are a number of genes that are activated by UV-A; hemoxygenase, collagenase and others. The list is pretty long.

So it depends on what we are observing.

Now, the second set of data that I wanted to share with you is dependence of HIV promoter activity on dose. And you can see the doses--first of all, there is a threshold. With low doses, there is no effect and there is a safe region, if you will. But at some point the activity starts to go up and the doses are not very high. This UV-B radiation there is only 1,000 joules per meter squared. According to ACGIH, radiation at 313 nanometers, typical for this range, should be safe up to 5,000.

So these are the two slides that I wanted to show. Thank you very much for the slides.

And I would like to add a few more things. The new developments in photobiology indicate that relatively low doses of UV radiation may be immunosuppressive--may be luckily immunosuppressive--and here I would like to let me just mention as a problem for analysis that as we look at the cervix we can think about possible effects on HPV present in this particular location and we have to think about Herpes infection.

One more word about UV-A and its safety. I think it's very dangerous to say that UV-A is safe because of the facts that I mentioned; activation of different genes, and recent work that indicates that UV-A may be a component in melanoma genesis. There are animal studies that indicate that exposure to UV-A is very effective in development of melanoma.

As we look at the spectrum of UV radiation, we prefer to look at this as a continuum, not as safe regions/unsafe regions, and I think it's appropriate when a device is analyzed to analyze the particular situation with the emission spectrum, with the power at different wavelengths and then the juice, whether this exposure is safe or unsafe.

The other two or three comments that I wanted to make is that we have to remember that there are special cases that might be particularly sensitive to optical radiation, UV radiation. This was mentioned yesterday, but I think it's worth mentioning it again.

There are patients with diseases that make them photosensitive--porphyrias, lupus erythematosus, not to mention xeroderma pigmentosum, and a number of other diseases that can make those patients particularly sensitive.

Then there are patients on photosensitizing therapies. Some were mentioned yesterday, but at this point a lot of different drugs in combination with optical radiation are used in oncology. Photodynamic therapy is expanding area of medicine, and these drugs should be taken into consideration.

Finally, there is a list of drugs that are not meant to be photosensitive, but they are. Photosensitivity is simply the side-effect of their use. Erythromycin is a classical example, but the list of them goes for 60 or 70 at this point is recognized by our colleagues in Center for Drugs.

Thank you very much.

CHAIRMAN EGLINTON: Thank you.

Before we go on to the formal discussion questions offered by the FDA, Dr. Solomon had a question that she wanted us to consider, which would bear on the rest of these questions.

DR. SOLOMON: I guess, if we are going to review this document, I would like to just go from the very, very broad perspective down to the more minute aspects of the protocol itself. The first question that comes to my mind is, is the framework appropriate? Have you identified the different possible indications of use for such instruments?

Any comments?

[No response.]

DR. SOLOMON: Well, then I guess--

DR. ANACONE: My name is Bob Anacone from Medispectra.

Dr. Burke introduced a couple of other indications this morning that were not listed in the draft guidance document. Dr. Burke, do you want to comment a little further on those?

DR. BURKE: There are other areas that this light can be applied to besides the cervix, and that includes the vulva, particularly when we are thinking of vulva intraepithelial neoplasia, and the same problems that we have on the cervix about low-grade/high-grade, significant/nonsignificant, we still struggle with both the colposcopic appearance as well as the histopathologic definitions. Whether or not this particular technique can be applied there was something I just popped off the top of my head this morning.

One can also go to things like Barrett's syndrome in the esophagus. This technique should be considered again. Things that are analogous to what we struggle with on the cervix there are other mucosal areas that have the same problem and, therefore, one could amplify its use into

those areas.

DR. SOLOMON: But in those instances, even though you are changing the site to which you are applying the device, the indication would be to identify a biopsy site.

DR. BURKE: Yes.

DR. SOLOMON: The most appropriate biopsy site.

DR. BURKE: Exactly. Yes.

DR. DAVEY: A few of the things, just looking at the list here that have been mentioned, not only triaging the ASCUS Pap smear, but also some of the low-grade lesions. I think that has been brought up by one or more individuals, using it to examine prior to CONE or loop excision. That was one of the things mentioned, and the question of a high-grade lesion localizing biopsy sites I think that also has been brought up. So I guess we should decide whether we want to add some words here.

To me it is very appropriate to use it for the low-grade, to consider the ASCUS and the low-grade because I think those are difficult, as we have talked about, to separate.

DR. SOLOMON: In terms of the triage.

DR. DAVEY: The triage.

DR. SOLOMON: Yes, I agree.

DR. DAVEY: And, also, I am not sure that there

would be any problem with using it to examine prior to a more extensive procedure like a loop. Does anybody else have any comments?

DR. LEVY: Actually, no; particularly in a referral population where the Pap smear and often colposcopy has been done by somebody else and they get referred to you, this is an ideal opportunity to verify.

DR. SOLOMON: Do you think we need to develop another indication or simply modify Indication No. 2 to encompass the possibility that it would be used to triage women for LEEP or not LEEP?

DR. O'LEARY: In many ways, that is more of a small variation, is it not, on Intended Use 3 for localized biopsy sites? It is someplace in between 2 and 3, but I wonder if the fundamental criteria that you would develop between those two couldn't be a slight modification of 3 to encompass the decision to biopsy or to LEEP.

CHAIRMAN EGLINTON: If Indication 2 became triage, period, that might handle it.

DR. DAVEY: That would include even a high-grade? Are we talking about even a high-grade lesion?

CHAIRMAN EGLINTON: Perhaps. I mean, it depends on--what we are talking about is opportunities to develop the protocol, and someone might develop a protocol using the

instrument, for example, for triage.

DR. DAVEY: Okay.

CHAIRMAN EGLINTON: I am proposing.

DR. DIAMOND: If we are going to be making broad guidelines, the other thing that I would think would be very helpful, which I think otherwise people would be very much confused in the future, will be the issue that was brought up yesterday by the first presenter from the audience dealing with the issue of the in vivo versus the in vitro test, and I would think we may be well suited to make a recommendation to the FDA that they make clear those distinctions between the two for the public and clinicians to understand. Because I think the fine line between them it is often going to get missed.

In other words the in vivo/in vitro distinction.

DR. SOLOMON: In terms of the reference standard, is that your point, that is used for the different in vitro versus in vivo devices?

DR. DIAMOND: What they are being utilized before. Because I think in the future people are going to take the in vitro tests and try to utilize them for some of the same things as we will be discussing further today. And that, as I understand it, was not the intent under which those products became available, and I think that can lead to a

large source of confusion for the public at large.

DR. KATZ: Perhaps I could just elaborate on that.

I think one of the concerns is that there is no gold standard because of the imprecision in in vitro assays, and so one of the interpretations that I made of this issue, which I think is an important issue as well, is how can one calibrate this new methodology in the absence of an accurate and precise standard, which is basically one of the concerns of the current in vitro methods.

CHAIRMAN EGLINTON: Colin?

MR. POLLARD: I appreciate both of those points. The one thing that I will assure Dr. Diamond and the rest of the panel is that we have been coordinating with our Division of Clinical Laboratory Devices, and given some of the comments yesterday and today, we will definitely be examining that very carefully to make sure that there is no misunderstanding and that there is a defensible consistency between how we are dealing with these different products across the board.

DR. DAVEY: I think that there has just been a lot of miscommunication and education about the in vitro devices, and I don't think any of the professionals using those would say that the Pap smear has been fixed by these in vitro devices. There is a large public campaign to

promote regular Pap smear screening. So I think that if that word has gotten out, that doesn't have anything to do with the FDA panel or professionals in that area.

DR. ROBINOWITZ: I'm Max Robinowitz. I am a pathologist in the in vitro side. I just wanted to point out that three of the members of this panel are consultants on the in vitro side, and I think the issue is how do you diagnose the cancer and whatever means possible will be employed, and we are doing our best to try to coordinate the whole continuum from in vitro test, in vivo test, and whatever can be done as far as a reference methodology, and that is why Dr. Hirsch spoke yesterday, and we are trying to coordinate this and clarify this as much as possible. And all of these deliberations will be available to the public, both the professional and lay public.

CHAIRMAN EGLINTON: Thank you.

DR. O'LEARY: The first communication from yesterday I think was misleading as to the intent of the panels, when they recommended the approval of the adjunctive in vitro devices. Since I framed the wording of that particular approval, I think it is quite clear to me, at least, that the wording that we intended, that we were hoping for some greater restraint in advertising than has been found and apparently than FDA's Division of Compliance

is willing to enforce regarding at least one of the advertisers.

But it's that advertising not the FDA position which has been the source of confusion here, and I don't think it is appropriate for the FDA or for this panel to be swayed too much by an excess of advertising in making its decisions on how to frame what might be appropriate ways of dealing with this from a regulatory perspective. We might hope again for greater activity of the Division of Compliance in this particular arena commensurate with the level that they've shown in certain other arenas of in vitro diagnostics, and perhaps that is the appropriate way of resolving those issues.

CHAIRMAN EGLINTON: Thank you. Let's move on to our discussion questions here and then have other comments as necessary.

Can we have comment, please, on Question No. 1. Are you going to put the questions up? There we go.

DR. DAVEY: Could I just ask, we are supposed to be taking notes. Are we finished with Diane's additions to the indications in terms of--because I don't want to--

CHAIRMAN EGLINTON: Are you satisfied that we are finished with that discussion?

DR. DAVEY: What I have taken away from what has

been said is for No. 2 we are going to expand that just to a question of triage generically.

DR. SOLOMON: Right.

DR. DAVEY: And for indication, Intended Use No. 3, localized biopsy sites we should just take into account that this may include sites other than the cervix.

DR. SOLOMON: Okay.

DR. DAVEY: Were there any other modifications that were suggested that I didn't catch?

And the LEEP would be--

DR. LEVY: Add to No. 3.

DR. DAVEY: So either prior to biopsy or LEEP are we going to say examination prior to or is the LEEP part, part of No. 2 or are we not even going to use the LEEP?

DR. SOLOMON: Well, I guess, to me it is more a question of triage; are you going to LEEP or not LEEP?

DR. DAVEY: Okay.

DR. SOLOMON: Triage to a certain therapeutic.

CHAIRMAN EGLINTON: That is why I was trying to leave it a little more open. We are not trying to write somebody's protocol for them. We are just trying to provide some guidance, and they may fit a very neat protocol in under Intended Use No. 2 if we just say generally a triage.

DR. DAVEY: Okay.

DR. O'LEARY: May I suggest that we back off, though, and not consider indications other than cervix? I think that that broadens the discussion beyond that which could be reasonably handled today.

CHAIRMAN EGLINTON: I think that is probably fair. We are not going to be able to address something as broad as the entire human body.

So I think we finished that. Dr. Davey and Dr. Katz are taking notes for us to make sure that we wind up at the end of the day with appropriate commentary to go forward and edit this.

So we are on to Question No. 1. Does anyone have any comments?

DR. NEUMANN: Mr. Chairman, I would like to comment on the electrical side of the safety issue. I think the document really refers to some very general aspects of electrical safety that are appropriate for any medical device, but really don't cover the issues, especially in the case of the device we heard about yesterday that applies an electrical pulse to stimulate or whatever it does to the cervix and then looks at relaxation time.

There is a great deal of work done in this area in applying electrical stimuli to other electrically excitable tissues in the body, and I think, first of all, it is

important that the FDA and the manufacturers are aware of the literature in this area and make sure that their devices comply to what is accepted there.

And the issue is more than issue of electrical shock. I think that is really a nonissue, when you get right down to it, unless you are applying this thing to a cardiac patient.

The issues are issues related to what happens at the stimulating electrode and what that does to the local tissue.

Several things can occur, and I don't think it's appropriate to go into a lot of detail here, but I think it is appropriate to look at the electrochemistry, to look at the electrode materials themselves.

The manufacturers should be able to discuss what is going on electrochemically as the charge goes from the electrode to the tissue because a redox type of chemical reaction has to occur, and this will produce what is called polarization ions, and these may be innocuous or otherwise.

And I think these issues really, really need to be addressed.

CHAIRMAN EGLINTON: Do you have any--off the top of your head--any appropriate standards or discussion documents for reference or can you provide those later?

DR. NEUMANN: I am not aware of any standards. I do know that the neural prosthesis program of NINDS at NIH has several contracts that are looking specifically at the effect of electrical stimulation on skeletal muscle and nerve. I can give the FDA the name of the person who is in charge of those contracts, and they might want to contact him.

CHAIRMAN EGLINTON: Is that specific enough, Colin?

MR. POLLARD: Sure.

CHAIRMAN EGLINTON: Dr. Hirshorn has a comment on this?

DR. HIRSHORN: Dr. Hirshorn from Polartechnics.

I would like to support the comments that you are making, having spent much of the last 17 years in electrical stimulation area.

There is no applicable standard, but there is literature, and I think that the guidelines should require manufacturers to discuss the safety of the electrical stimulation on the localized tissue, and I think some wording just as simple as that would be appropriate. Because there isn't a standard one does need to look at such places as NIH nerve stimulation area or in other areas to look at polarization and so on.

So I think some wording that just says that the manufacturer should provide data to support the safety of electrical stimulation on the local tissue would be appropriate for the document.

CHAIRMAN EGLINTON: Thank you.

Is there any commentary on the optical radiation portion of this?

Dr. Diamond?

DR. DIAMOND: I don't know if it really makes a difference, but depending on the type of devices that are utilized in the future I think the manufacturer should pay attention to any difference that may exist for the ectocervix and the endocervix for squamous cells and glandular cells if there is cervical mucous present, if there is inflammation present, and how any of those variations may affect these different properties.

CHAIRMAN EGLINTON: All right.

DR. O'LEARY: I have a question that perhaps somebody can answer. It seems unlikely, but given that some of these devices may employ both electrical stimulation and illumination of various sorts, are we concerned about thermal injury effects? Is there a possibility of having thermal effects as a result of simultaneous combined stimulation that we might not see with either modality

alone?

CHAIRMAN EGLINTON: I guess that would be for the manufacturers to demonstrate that there is not such an effect.

DR. O'LEARY: Well, I think it is really aimed at FDA, just to know that they have thought about that question. It may not be significant enough to have it in the document. I have no idea.

CHAIRMAN EGLINTON: It seems that Dr. Biers and Dr. Lebovitz could comment in this area adequately after the panel meetings to make sure this is edited appropriately.

MR. POLLARD: Dr. Biers is not really comfortable talking about the thermal effects. That is not his area. But I think, suffice it to say, that we will look at that and make sure it is not a concern, and whether we build that into the guidance document or whether we resolve that beforehand, we will definitely take care of that issue.

CHAIRMAN EGLINTON: I just meant this whole area, this whole question here, probably the people most qualified to comment on this question aren't sitting at these two tables. They are probably sitting in the audience.

MR. POLLARD: I don't want to speak for Dr. Biers on the optical aspects. Maybe you would like to, Yonish, say something. I think my understanding is that we were

taking some of those comments earlier today and yesterday very much into perspective and, in fact, we may end up working with one or two of those folks to make sure that we develop that section appropriately.

DR. YIN: We do have people in FDA that works on that because in my division we are taking care of electrical stimulation for the cochlea, so we do have the right people, but they are not sitting here. So we will take care of that issue.

DR. NEUMANN: I think related to that, a good reason that this should be included in that someone down the line may, in fact, want to thermally provoke the cervix to amplify differences and, in that case, then, what Dr. O'Leary has mentioned would definitely be a problem.

CHAIRMAN EGLINTON: Dr. Biers?

DR. BIERS: Regarding risks from optical radiation, as I mentioned before, I think it needs to be analyzed on a case-by-case basis because the sources have totally different emission spectra. If a source is invisible range, then our concerns would be very low. If the emission is in UV-B, then probably using the numbers from ACGH standards is appropriate.

UV-A at this point is an open area of open discussion. It is not very clear. My feeling is that the

amount of tissue that is exposed is very small and probably those risks are not very high. One thing that needs to be taken into consideration is the depth of penetration. UV radiation, invisible radiation the penetration depends very strongly on wavelength; shorter wavelengths, shallow penetration and longer wavelengths the radiation penetrates much deeper.

These are the factors that need to be taken into consideration.

I think that from the viewpoint of since the issue was raised of HIV infection, my feeling is that this should not be a big issue, the reason being that the amount of the virus in the exposed tissue is very, very small as compared to the viral amount in the entire body. So activation of this small amount of virus should not be of great concern.

I have no good answer regarding the papilloma virus. This is the local situation. This is the tissue of concern. If UV-induced immunosuppression may stimulate HPV, then this might be a problem. But, again, this will depend on the emission spectrum and spectra irradiance of every individual device.

Thank you.

DR. KATZ: Just a follow-up on Dr. Diamond's comment on whether the cycle phase will influence the

assessment of safety, as well as function itself of the devices, and how we incorporate into not just our standards for safety evaluation, but later on in the actual design of some of the evaluation proceedings.

That is a question as well as a comment.

DR. O'LEARY: And back to thermal, and Dr. Neumann's comment on my own. On reflection, I think the thermal absolutely needs to be included, and the reason is because the group of Ramand devices that was referred to but not talked to specifically are probably going to use infrared radiation, which is basically a heat source, and I do Ramand spectroscopy, and I don't want to get my hand in the way of the beam the intensity is so--I'll burn myself.

CHAIRMAN EGLINTON: Thank you. Are there any other tissue effects that anyone wants to discuss? The question is what kind of tissue effects should the FDA be concerned about. Have we mentioned all of them?

[No response.]

CHAIRMAN EGLINTON: What study models are appropriate for testing these kinds of effects? Does anyone care to offer--

Dr. Schiffman?

DR. SCHIFFMAN: How about cutaneous wart disease or mucocutaneous wart disease and other places where it is

unexposed? I don't have any design, but there is a dermatologic literature that I don't know on HPV and other skin surfaces that should be at least assessed.

CHAIRMAN EGLINTON: I'm not sure, Dr. Schiffman. Are you talking about for assessing the effect of these devices on mucocutaneous lesions?

DR. SCHIFFMAN: It is just that people are worried about application to the mucosa, but almost nobody ever draws reference to the other HPVs that are not genital. They are cutaneous and, therefore, exposed to solar energies and whatever else people work with; infrared, people with warts. I don't know what is known. The dermatologic literature on common warts is not that--I tried to review it once. There is not that much and a lot of it is old, but I just thought it should be mentioned as part of the review for safety that there is some literature on whether people who work outside get more intensive like local immunosuppression of the skin in relation to cutaneous wart disease. Is that known? I don't know, but somebody knows.

DR. O'LEARY: I am almost certain it is because I believe that there are medical devices now that have as an indication for use, and I know that they are being used to treat cutaneous warts as well esophageal warts. So I suspect that that literature is not only known, but this

division is well familiar with this.

CHAIRMAN EGLINTON: All right. Study models, does anyone have suggestions for study models that are appropriate for testing these kinds of effects? One suggestion Dr. Katz made some sort of study of different effects at varying times in the menstrual cycle.

Dr. Hirsch?

DR. HIRSCH: From a statistical point of view, when we are talking about studies that are designed to look at safety, one thing that we have to pay attention to is that adverse events occur rarely and to observe rare events you need to have a very large sample.

I think there are a couple of changes to the guidance document that might reflect that fact. One is under the feasibility study the second point of the feasibility study on page 7 of the draft the language is that the study should also be able to demonstrate that when the device contacts the cervix it does not damage the tissue, it does not affect the results. That is too strong, certainly for a feasibility study, and probably too strong for a study of any kind.

I think that the guidance document would address the reality of looking at safety issues by confessing that it's going to be able to find only the most common adverse

events, and to find these unusual adverse events really is a domain of post-market surveillance, which I think that CDRH can have as part of a guidance document as part of an approval package, a plan for some sort of post-market surveillance.

Also, to give you kind of an idea about how hard it is to find adverse events, have you ever been in a meeting with a statistician and a statistician seems to be able to do light-speed math and come up with impressive kinds of things. We have some tricks, and I will tell you one that has to do with adverse events if you promise not to tell anybody else. That is called the Rule of Three. With the Rule of Three, there are two ways to use the Rule of Three; one is when you don't see anything bad how sure are you that the event is rare?

The way that that Rule of Three works is you take three and you divide it by the number of observations that you had, the number of people who were potential for adverse events. So that if you have a study of size 100 and you don't see any adverse events, to be pretty sure that you are including--95 percent sure, in fact--that you are including the actual frequency of adverse events, what you need to do is you need to consider a true frequency of at least 3 percent--3 divided by 100--and you can work that backwards

to figure out what kind of sample size you need.

So if you think that these adverse events that are of concern for this device occur one out of a thousand, the number of observations you would need to have to have a pretty good probability of seeing an adverse event is 3,000--certainly beyond the scope of any feasibility study or probably any study that the FDA could require of a manufacturer of one of these devices.

So I think that the guidance document should include those kinds of confessions of reality rather than setting a goal that really won't be able to be achieved.

CHAIRMAN EGLINTON: Dr. Biers?

DR. BIERS: I wanted to add a few pieces of information regarding immunosuppression that may be induced by optical radiation.

This area of our knowledge explodes at this point, and it started from observations--classic observations--on flare-ups of Herpes lesions when people were exposed to substantial amount of sunlight. But at this point there is a number of experiments conducted in animals that indicate immunosuppression that can be readily induced with UV.

And then this information is also basis of some techniques that I experimentally used in the clinic, like in transplantology to suppress rejection of transplants UV-B

radiation can be used.

How big doses are needed to produce this immunosuppression is not quite clear. Until recently, it was considered that the dermatological doses of radiation used to treat psoriasis and other skin conditions are not immunosuppressive. Recent data indicate that after longer follow-up there is increased incidence of skin cancers, and it is in analysis tied up to possibly immunosuppression at the time of the treatment.

There are good data on Herpes. There are good data on HIV. I haven't seen good data for papilloma. I am not aware of good model for mucosal studies. Obviously, thinking that the cornea is better tissue to analyze than the skin makes sense to me. However, mucosal tissue is never exposed to optical radiation under normal circumstances, so it is a tissue that lives under different conditions.

We were trying to develop a proposal for studies on mucosal sensitivity to optical radiation. We had problems with designing the study. It was under consideration. We haven't done anything yet.

Thank you very much.

CHAIRMAN EGLINTON: Thank you. Does anyone have anything further to offer on specific study models

appropriate for testing the biologic effects?

DR. O'LEARY: I don't think the studies, quite frankly, are going to be doable by the manufacturers. I think if you were to reality test this for reasonable levels of adverse effects, the kind of stimulation and so forth, I think we have got to ask the manufacturers to go with the best, most current literature available, and what is tolerable may depend a little bit on the indications for use as well because, as a primary screen, you are looking at one thing for making a decision as to which site to biopsy when a biopsy is already going to happen, maybe something else.

But I think to ask for studies beyond literature, given what the likely risks are going to be and given the level of the literature that is out there and then the resources that a manufacturer would likely be able to bring to bear, may be a tad unrealistic. We just heard about a local study design problem. Manufacturers will have no less of a problem. I think it might be an insurmountable burden.

CHAIRMAN EGLINTON: Ms. Domecus?

MS. DOMECUS: Just another point on adverse events, to make sure the panel is aware of, is that all manufacturers and actually user facilities that are required to report to FDA in the form of what is called an MDR report asks for serious injuries.

So if we don't place a burden of 3,000 patients post-market surveillance study on the manufacturers, it doesn't mean that there is no mechanism for FDA to capture adverse event data once the products are approved.

CHAIRMAN EGLINTON: Dr. Yin?

DR. YIN: I'd also like to hear the panel discussion whether animal studies will be apropos; you know, a certain amount before they even venture into human. I would like to hear the discussion.

DR. O'LEARY: The problem I have with the animal studies is that it seemed like we would have to go to primate studies because I think the cycling effects are at least potentially important. If you have made the decision to go on to primate studies, then we have to deal with a primate that is large enough to accept the device under consideration.

And then to find an adverse effect, we would probably have to use the captive primate population of the United States. I don't think we have got a female--I just don't think we have a feasible model for adverse effects in primate studies. That would be my concern there, again, is insurmountable burden.

CHAIRMAN EGLINTON: Dr. Richards-Kortum?

DR. RICHARDS-KORTUM: I think there are some other

optical standards that we can take a look at that exceed the elimination of a colposcope. In a colposcope you have got a little 20 watt light bulb, which is illuminating the cervix. But if you look at endoscopes, which are routinely used to eliminate mucosal surfaces, those are using 1,000 watt xenon lamps, and so there are accepted medical techniques where mucosal surfaces are exposed to a lot of light. I think you can use those as standards for comparison in relative risk analyses to compare to the ACGIH standard.

Woods lamps are another example where UV light is used to illuminate mucosal surfaces. So I think there are some other standards that could be incorporated.

CHAIRMAN EGLINTON: Dr. Diamond?

DR. DIAMOND: I think you could do and should do some basic safety studies in animals. I would agree I don't think you can do the extensive ones, but to do some simple ones to look at tissue effects is very easy to do, and if you are going to do it in an in vitro model or simulated models, where if you can't go--for example, in the rabbit, it would be hard to go through the vagina, but you can do a laparotomy, open up the vagina, expose the cervixes, and then expose them to optical light, and then suture everything closed, come back a couple of weeks later and look and see what effects are in place and to do that before

you expose women to those sources.

CHAIRMAN EGLINTON: Additionally, I know our own HPV lab at Georgetown, Dr. Schiffman knows well, uses a--I mean they must use pounds per week of foreskins, and you can use large tissue, and they have immortalized a number of cell lines in HPV research. So there is a lot you can do with human tissue. It may not have blood pumping through it right now, but they can keep it vital for some length of time.

DR. KATZ: I think that biologically we have to be careful in these choice of animal models. A rabbit vagina histologically is very different from a woman's vagina, and it causes great problems in other types of analogous testing. From a research point of view, there is a real need to sort this out in terms of what is available to uso. But do we know enough today, other than the notion that primates have menstrual cycles, so, in that regard, they have some similarity to people; whereas, most of the other animals do not. Do we know enough to really--what can we say about the accuracy of animal models and how does that get incorporated into a document like this?

CHAIRMAN EGLINTON: Any other comment on animal models?

Dr. Wright?

DR. WRIGHT: I spent three years of my life at Harvard painting bins pyreen on mouse cervixes, and I can tell you that there is no acceptable animal model for looking at interactions in the carcinogenic sequence in cervical cancer. It involves human tissues, it involves human HPV, which is very tissue specific, those interactions, and when you talk about doing a model system, it is going to be important to take all of that into account as simply not available.

CHAIRMAN EGLINTON: Thank you. Any other discussion on Question No. 1?

Mr. Pollard, have we answered enough?

MR. POLLARD: Yes.

CHAIRMAN EGLINTON: We will move on to Question No. 2.

Are there any other possible adverse effects that might result from the use of these devices that we have not already included in the draft document?

We did include thermal as something that is not listed here.

DR. LEVY: I just think, again, we need to add in there that the effects are both to the patient and to the operator.

CHAIRMAN EGLINTON: Right. I know we have

discussed the visible range and the applicability of the standards to the eye, and I think that is pretty well covered.

DR. LEVY: That is for these particular devices, but there may be others that--for example, Dr. O'Leary talked about that we might want to just have it covered for the circumstance in which it is something a little different than we are looking at today.

DR. DIAMOND: The manufacturer might also want to specify if a patient was pregnant early in pregnancy and perhaps didn't recognized it, or even if they did recognize they were pregnant and were having a test done, would the device being utilized have potential adverse effects on a pregnancy.

CHAIRMAN EGLINTON: And this again probably would be more important with something other than just a photo device.

DR. DIAMOND: Yes, something that might come up in the future.

CHAIRMAN EGLINTON: The transcriptionists are having some trouble picking up everybody's voice so please talk directly into the microphone.

Question No. 3 is the intent here to talk about each of these four different indications and go through all

of these questions for each indication? Colin, is that what we are after?

MR. POLLARD: In general, that is how we laid out the questions. I think if there are areas where it is the same, we would ask that you maybe indicate so.

I think Diane's question that she added on really may shed some light because hers was a general question; how about the overall framework? The overall framework was organized along the possible different indications for use this technology could take, and so that is how we kind of developed this document.

CHAIRMAN EGLINTON: Did anybody else follow Colin? Am I the only one who didn't? Did everybody else follow him?

MR. POLLARD: I guess what I am saying is, if the panel is comfortable with the framework of the guidance document right now, that is certainly something that we need to know up front. If they are comfortable with an indication-by-indication approach--we didn't see another way to do it, but maybe there is a better way to do it.

But within that context, we want to be able to give some specific guidance to companies, depending on which direction they take with the technology, so we would like to give, if not protocol details, at least protocol comments or

suggestions, that kind of thing for the different indications.

CHAIRMAN EGLINTON: So, it seems to me, we need to start with Indication No. 1 and go through each of these questions.

Dr. Davey?

DR. DAVEY: Yes. I don't know that I have an answer to this, but I just wanted to bring it up before we get too much into the different details. It is sort of another question like Dr. Solomon had, and that is are we comfortable--basically, we talked a little bit about one-armed versus two-armed approaches yesterday. I think we need to maybe bring that up again today.

Basically, I think most of these are in one patient group comparing what would happen with and without the device. For some of these, and I don't know that I have the answer, is it appropriate to have a two-armed study? I would like to just open that up maybe before we get into details.

CHAIRMAN EGLINTON: We might discuss that with each indication? I mean, is there one indication--

DR. DAVEY: We could, but I think that is another question. A couple of other questions/comments that I had, too, is, as we get into this, what kind of Pap is going to

be used as the reference Pap since we have so many cervical vaginal cytologies. I think we will get into a little bit more about how we define a patient as negative, and maybe that gets into the reference diagnosis and how we define a patient as abnormal. I think those will come up as well.

CHAIRMAN EGLINTON: Why don't we just go ahead and start with Indication No. 1 then and see if we can pound through these questions with that one, including the concept of reference standard, different types of Pap smears, whether or not that needs to be a two-armed study and so forth.

So if we look at Indication No. 1, adjunct to the Pap smear, what are the appropriate study subject inclusion/exclusion criteria, and we have some suggestions here; a description of patient population.

Do we have overheads of the actual draft document that we can put up there? Everybody has the document. We have inclusion criteria listed; one, women who are candidates for a Pap smear, exclusion status post prior total hysterectomy.

Does anybody have any comment on this particular intended use in terms of inclusion or exclusion?

DR. LEVY: Gary, I think we need to address the issue of pregnancy at this point because I think this will

affect us all of the way through these studies.

CHAIRMAN EGLINTON: Right. Is everybody comfortable suggesting that we ignore pregnant women at this level study, the initial phase of studies of these pieces of equipment?

Dr. Davey?

DR. DAVEY: Yes. Just to comment, it seems like so little is known about multiple states. I don't know if this is appropriate to put into these areas or the feasibility. But at least at this point it would seem like excluding pregnant. We also have to know more about how these devices react, different transformation zones, if there is a polyp, if there is bleeding going on, severe inflammation, and so you don't know really whether you can exclude some of these things until you know how it reacts to begin with, and I don't know if that is part of the feasibility or the indication exclusion for inclusion for the later study.

DR. O'LEARY: I think it's worth taking a lesson from drugs in this case. I think the idea of suggesting the exclusion of pregnant women is reasonable. If you remember your PDR, almost all of these things say that, "We haven't established safety effectiveness in pregnancy or in fetuses," and that is probably sensible from the standpoint

of actually getting through the process.

No doubt, off-label use will answer those questions in the long run.

DR. SOLOMON: I'd also like to draw a distinction between what are suggested inclusion and exclusion criteria and what the particular intended use of the device is. I think there is a paragraph at the top of page 9 that emphasizes that the types of patients selected for inclusion into the study are going to depend on the intended use and indicated uses claimed for the device.

So that, to a certain extent, it's going to be up to the discretion of the company whether or not to include pregnant women, depending on what they intend as the use of the device.

I am not sure that in a guideline like this we should be so prescriptive as to dictate what that would be.

CHAIRMAN EGLINTON: Dr. Diamond?

DR. DIAMOND: I think the other issue that needs to be considered is that, if a protocol were to come from a company to our IRB--Institution Review Board--which I also sit on, which said they exclude women who are pregnant, the question would be why because there are currently federal guidelines that prohibit excluding groups of patients for situations like pregnancy.

And for us, therefore, to ask FDA to put that into the guidelines, I think you need to look at that in the framework of those guidelines which become an issue in virtually every meeting that we have about should women be excluded or should pregnant women be excluded from individual protocols, which are often company sponsored.

DR. DAVEY: So maybe we just need to add some wording then that the manufacturers need to consider all of the possible disease states and then either present information about excluding or including women for specific uses, and then maybe we just need to add some more things in there; you know, infections, bleeding, different times of the cycle and so forth.

DR. O'LEARY: But I think it's reasonable to ask for exclusion in the feasibility study phase. In general, you look at pregnant women as being a higher risk population for whatever. And in feasibility studies I can't imagine any feasibility study in any other area where pregnancy wouldn't be an exclusion, except for those cases where one was doing something pregnancy specific.

CHAIRMAN EGLINTON: Right. But at this point we are talking about we are beyond feasibility when we are talking about indications for use at the point of the draft document where we are discussing. That is a strong point.

DR. LEVY: I think the issue that we talked about with pregnancy was the issue of bleeding and patient perception. We don't necessarily have to exclude patients in the protocol, but allow them to exclude themselves if they are uncomfortable when they read the informed consent document.

Similarly, with respect to the reference point that we use, obviously, if we are using LEEP or CONE as a reference, then that is an inappropriate thing in most pregnant women. On the other hand, small biopsies are not contraindicated in pregnancy. So I think we might solve this issue by carefully drafting the informed consent document and allowing patients to self-select for or against the study.

CHAIRMAN EGLINTON: And, also, all we are editing here is a proposal, a guidance document. We are not really writing somebody's protocol for them. If they bring a PMA in here with a well- thought-out protocol and good justification for their inclusion/exclusion and that drives straight to the point of their intended use, that is great.

DR. DIAMOND: Gary, I think it's also going to be very important, although I am not quite sure how you put it to the protocol, that in the study population that ends up being studied at the time of the PMA submission, you have to

have a sufficiently large number of subjects who fall into each of the different categories that we have been hearing about.

They can't all fall into normal or we won't have a discriminatory ability to know whether or not this adjunctive device has actually helped anything. I don't quite know how to build it into the protocol, but that is going to be, I think, a necessary part of the final submission.

CHAIRMAN EGLINTON: That also answers the issue for pregnant women as well. Nobody is going to bring a PMA in with seven pregnant women in it and then ask for labeling to use this in pregnant women.

No one is going to bring a PMA in that has 100,000 normal Pap smears, two ASCUS, and the rest LSIL and say, yeah, we'd like to use this for screening.

DR. DIAMOND: But I guess my point is I don't think in the end we can say you need to have a hundred women or a thousand women or just a certain number of women. I think the distribution of Pap smears those individuals have is going to be a key issue, as opposed to just an absolute number.

CHAIRMAN EGLINTON: Does anyone care to address the appropriate reference diagnosis for a comparison here

for Indicated Use No. 1 or is that what Michael is talking about?

Dr. Schiffman?

DR. SCHIFFMAN: For our natural history studies, we have spent sometimes months thinking about reference diagnoses, not for screening applications. That is a secondary issue, but just to so-called seek the truth. So I am familiar with this.

And we have had, actually, a conference on this topic among all of the PIs in our study, both pathologist clinicians, but I still want to be brief about this.

So what we did, as I said yesterday, was to ignore the idea of LSIL plus, which is mentioned in the hypothesis here. Because in heavily screened populations if LSIL is five to ten times more common than HSIL, that combination could allow one technique to pick up more of the low-grade lesions, miss more of the high-grade lesions and still be pronounced sort of superior to--

Since I so heavily weight HSIL, I really think that that LSIL plus, which is sort of based on the CIN scale model, has to be questioned, hopefully, in favor of a dichotomous model, where low-grade is considered infection and high-grade is weighted as real pre-invasive cancer.

So what we do to ensure that, and this applies to

all of the population-type studies, is we take the conventional Pap smear, but we take the implement and put it into preserve-set or any other buffer--Roche buffer. That allows a second totally independent cytologic evaluation as well as a virologic evaluation. This is all headed towards gold standard.

We also use a visual technique, which might be, in this case, one of the test technique, but in our study was cervicography. If anything is abnormal on the two cytologies or a visual technique, the person goes to colposcopy, plus a random sample go to colposcopy of the total normals.

So now we have a population approaching final definition by, and this is just for HSIL, of histology. Now, the question with histology and high grade is not specificity, as we heard. It is what if they missed, what if the lesion was missed by the colposcopist, so you are not picking up all of the high grades.

If both cytologies have said high grade and there is no high grade histology, that person goes to LEEP because there is a cyto-histo lack of correlation that could be dangerous. With that model, we feel like we are capturing most potential high grades histologically, and that is our reference standard--histologically confirmed high-grade

disease.

And we found that LSIL just cannot be handled. Fewer than half of our sure LSILs cytologically and by every evidence are histologically confirmed, and so it is an extremely difficult gold standard.

So this approach is really very tedious, but maybe we can derive some proxy of all of those reviews, and there is all levels of review and everything. I didn't discuss it, but I feel like you are going to need more than one cytology, and you are going to need some sense of adjudication of cytology histology lack of correlation.

DR. DAVEY: Yes, I'd like to agree with Dr. Schiffman. I think we need, first of all, to define somebody as negative, we definitely need more than one path. I mean, if it is going to be used--and we are not talking maybe about this indication, but it would be nice to have more than one test, other tests, to define a patient as negative. So either a history or other tests done at the same time, and I think for abnormal you can't just rely on one colposcopy. If there is something funny, you may need to go to LEEP, and you probably need to have adjudication on anything that is not an obvious high-grade lesion, and possibly even those.

CHAIRMAN EGLINTON: Dr. O'Leary and then Dr.

Hirsch.

DR. O'LEARY: I think that we need to focus very specifically on the indication in this case. I think the risk that we are looking for and the reason that the hypothesis asks for not a significant decrease in specificity is because going to additional LEEPs is considered an adverse effect. If that weren't the outcome, then there would be virtually no adverse effect to consider and just an increase in sensitivity would be sufficient to be an indication for use.

If that is true, then, the first question for the gynecologist--because I am not going to try to answer this question--is are you comfortable if we use high grade alone as a reference end point and basically saying we don't need to treat by LEEP any lesions which are currently being classed only as low grade?

Otherwise we have go to for perhaps a bad use of low grade. But it has to fit into whatever current standard of practice that the gynecologists on the panel are comfortable with using, and I'm not sure that we should be pushing for what sounds to me a little bit, Mark, like almost a change in the standard of practice--something that may be appropriate, but is probably--

DR. SCHIFFMAN: There is no standard practice.

DR. O'LEARY: Well, that is what I am asking.

DR. LEVY: I guess as the only real practicing gynecologist sitting on the panel I will try to address this.

Mark is right. There is no standard of practice. The real issue is not that I have any problem at all following a low-grade lesion because I absolutely agree that those low-grade lesions are really medical illnesses. The real issue is what we saw this morning, that among the low-grade lesions, there will be somewhere between 10 and 15 percent that really represent high-grade lesions, and what are we going to do with those people.

In practicality, whatever protocol we come up with, when we identify people with low-grade lesions in the study population, they will be followed at some point in time, whether that be three months or four months or six months. They are not within the study protocol going to be lost to follow-up.

So I would be entirely comfortable doing this dichotomous decision tree with the presumption clinically that the people who fall into the medical group do get follow-up. In other words, we are not talking about a population in Costa Rica right now who may disappear into the mountains and never be seen again. We are talking about

a group of women who have elected to participate in a study and have agreed to the appropriate follow-up. So I really wouldn't have a problem with dealing with the high grades in one way and looking at the low grades in another way.

And, in fact, we could use these study protocols to determine for ourselves clinically whether we can make a better distinction or not using the device. That is exactly what we want to do.

CHAIRMAN EGLINTON: Dr. Hirsch?

DR. HIRSCH: I have two comments. One comment has to do with what has just been discussed, and that is whether a dichotomy is better than getting more detail. And I think it is important to realize, from a statistical point of view that as you decrease the amount of information that you have in your outcome, what you are doing is increasing your error.

And something that is very common but incorrect practice is to respond to poor reproducibility by collapsing a scale. What happens when you do that is you actually increase the noise in the system. It appears to be something that is more reproducible, but precision is only an aspect of reproducibility. Reproducibility also reflects episodic agreement, which is, although it may look better, is not necessarily better.

So I think it is important to think about the level of precision or the level of detail not based on reproducibility.

The other point that I would like to make is that earlier, when we were talking about schemes for identifying the reference procedure and we were talking about adjudication of results and so on, that is resolution of discrepant results that you are talking about, which makes perfect sound sense when you are trying to get the best diagnosis for an individual patient.

But when your purpose is to characterize a diagnostic test, the pattern of increasing the precision of certain diagnoses is such that you are overly optimistic about the performance of the test. Now, that doesn't mean that that is not something that you should do, but I think that it may be that that gives you less than error than not doing that.

But I think that we need to be aware of what we are doing as we are talking about resolution of discrepant results and the distinction between studies and diagnosis of individual patients.

CHAIRMAN EGLINTON: As I listen to this back and forth, I can't help but think of home uterine activity monitors.

Now, we have a new tool, it's the greatest thing since night baseball. We are going to add this into our current practice. We all do Pap smears, and then we do something when the Pap smear result comes back. We do the right thing. Now we are going to have a new tool, and this new tool we are going to apply through the speculum to the cervix, and this is going to change our practice for the better. Our patients are going to have better outcomes.

Maybe just like Dr. Davey said, show me with a two-armed study. Maybe that is the most important thing to do with this thing.

Dr. O'Leary and then Professor.

DR. O'LEARY: To the question of reference diagnosis, I don't think we would have approved an in vitro device that we didn't believe would increase the yield of LoSILs that, if we went forward, we would have to ask for LoSILs to be at least the same and HiSILs up or HiSILs at the least the same and LoSILs up.

I think that is sort of the bottom-line philosophy that I think would have applied or would probably apply given the constitution of hematology and pathology. I don't want to speak for anybody other than myself. So I think that needs to be there.

I think the reference diagnosis problem and the

resolution of discrepancy problem is probably handled best by going and asking that any biopsies or any LEEPs that result from the use of the procedure and are used to determine the sensitivity and specificity be consensus diagnoses from the very beginning; that we ask for agreement of at least two out of three pathologists, and that we don't try to resolve discrepancies post hoc, but that we try to get a consensus diagnosis going in to begin with, understanding the fact that that may decrease--it only decreases but doesn't eliminate some of the reproducibility problems.

That would obviate some of the problems that we saw in the in vitro devices when we have discussed those.

DR. DAVEY: Okay. We're recommending as the reference diagnosis for any abnormality considered found by the device that it be the most severe, the highest level of abnormality found on any procedure? It may not be the initial, but it could be a follow-up procedure after that and that it should be adjudicated. Is that what we are saying?

DR. DIAMOND: I don't think we've concluded anything yet.

DR. DAVEY: Well, I would like to propose that we don't just use the results from one colposcopy procedure,

because if it is missed and it's found later on, then we need to consider that. So any additional histologic material within the time frame.

CHAIRMAN EGLINTON: Professor Coppleson?

DR. COPPLESON: Malcolm Coppleson, Polartechnics.

It is inevitable that lack of correlation between in vitro protection devices looking at the living tissue is not going to correlate with cytopathology and histopathology, looking at cells that are already dead. This will happen at times.

What can happen is that the in vivo device could, in fact, be getting it right in terms of the potential of the cells to become cancer, will be measured against what is clearly a fluid gold standard if we use histopathology alone and, therefore, will be penalized really for getting it right.

As Dr. O'Leary says, there are really two brass standards here, and I don't think--not even silver is what we look in terms of if we are looking at neoplastic potential, which is really what we want to know, and I would have thought the reference diagnosis would be better with a combination of two brass standards, which would then become a silver standard; namely, taking into consideration the expert views of colposcopists and histopathologists.

And, really, this is what is happening around this country at the present time in the best institutions. When there is a disagreement between the colposcopist and the histopathologist, they get together and they work it out, and they decide what should be done for that particular woman.

And I would think that it is probable that in this document we should be able to draw up some kind of decision tree where, where there is disagreement between the histology and the colposcopy, that they could come to a final diagnosis. And I would like to recommend that some effort be made to see if that could be made possible.

CHAIRMAN EGLINTON: Thank you.

Dr. Schiffman?

DR. SCHIFFMAN: There's probably many different valid possibilities. Another approach we have used, if you don't like adjudication, is we digitized the colposcopic images using one of the two available digital video techniques, and we have a dispassionate another reviewer--or actually two and with a judge if they disagree--as to whether the biopsy was taken in the right place.

What we do is we get those cases in which the biopsy was right on and those in which there was a chance, at least, that the biopsy appeared to be off from consensus

opinion. It gives us at least a weighting of the gold standard to know whether people are happy with that tissue or not, and it allows you to repeat the analysis with perhaps a less error prone histologic gold standard because colposcopy is intrinsic to pathology, and you have got to address the sense that colposcopy and the placing of biopsies is highly impressionistic, not 80 percent, but in our work with experts trying to all point out it can be very bad. It can be 60 percent, 55, 45 percent as to within .6 centimeters of the correct place.

So I feel like we are in a situation that, to get a gold standard, to even talk about things like sensitivity, specificity, we are going to have to do some work more than just a single measurement of any kind.

DR. DAVEY: Could I just ask, though, when you find these discrepancies, isn't the ultimate thing then to go back to the patient and do either a LEEP or another biopsy? So, still, aren't we coming up with another histologic--I guess that is sort of the thing I was getting at because don't we still have to have at the end some histologic--

DR. SCHIFFMAN: Well, you do or you don't. I was saying if you don't like correction, you can at least stratify your gold standard as to more likely to be gold--

DR. DIAMOND: Oh, I see.

DR. SCHIFFMAN: --more possibly not. I actually like Dr. Coppleson's, with a modification, I like the sense of, if this is a colposcopic impression machine, why not just compare it to a colposcopic expert system, an expert? So that the question would then just become does this machine give you a valid colposcopic impression, as if Dr. Coppleson were in the room or somebody else.

But the idea of combining anything through panels makes several of us a little--it is difficult sometimes. It is very time consuming and expensive to fly people in. So combining colposcopic impression and histology and then getting more tissue can take weeks and months. It is very difficult.

DR. LEVY: I think from a clinical standpoint that is very difficult. What we are looking at right now, though, is Indication No. 1, which is primary screening. So we really need three arms of this piece--

DR. DAVEY: It's adjunctive.

DR. LEVY: Pardon me?

DR. DAVEY: It's adjunctive.

DR. LEVY: Adjunctive to the Pap smear, excuse me.

But we know with Pap smears, for example, that a single cytological sample is inadequate to tell us for sure

that someone is normal. And, in fact, what we know is what we probably need is three, certainly two.

So the first screening here will be normal, low grade, or high grade, and then we can have follow-ups depending upon those. Clinically, I don't have a problem with even going so far as colposcopy and LEEP, even for low-grade lesions, recognizing that, for the most part, that is way overtreating people. But in this country at the moment, there are certainly plenty of people who are doing that and for the purposes of a study and to be sure that we have sampled the entire transition zone and that we are not missing something, I don't think I would have a problem with that in our study design as a way to be sure we are getting all of the tissue.

And then if we have a normal, in other words, our initial screen that's normal, we are going to have to have at least three points in time, I think, in order for us to say what we want to say about these devices because that is what we need to tell someone that they are really normal.

CHAIRMAN EGLINTON: Dr. O'Leary?

DR. O'LEARY: I don't think that is what we need to do. I think maybe we recast the question a little bit differently and think about having a result of the Pap smear, in some sense or another, as being refer to

colposcopy/don't refer to colposcopy.

And if we look at it that way and then considering the fact that we don't want to bias the statistical analysis of subsequent data by using a multiple resolution procedure, we would like to resolve things at the level of colposcopy and ask, from the specificity perspective, okay, at colposcopy was the colposcopy justified. The colposcopy justified could be a decision based on a consensus view of the colposcopic examination, including any biopsies that might be taken at the time of the colposcopic examination.

That is sort of the current practice and represents a simple combined single end-point study. It takes into account the visual impression. It takes into account the histopathologic impression. We can deal with consensus at that point, and we don't need to go to multiple end points. Although it doesn't answer every question we would like to know about the device, it answers the question that adjunct to primary screening, it seems to me, is really trying to get to, which is was this colposcopic examination justified.

DR. SCHIFFMAN: How do you handle low-grade lesions, though?

DR. LEVY: My same question is does that mean that you refer everyone with ASCUS and low-grade lesions for

colposcopy or that you eliminate all of those people from colposcopy?

CHAIRMAN EGLINTON: I think it has to be kept very, very simple. We are trying to craft a paragraph or two in a guidance document. Can you imagine now the manufacturers here with a PMA, how complicated is this going to be? I think Dr. O'Leary is right. Our guidance should be keep this very, very simple. If it is adjunct, it's an adjunct to the Pap smear. I mean, the current system is Pap smear.

Now you have a new tool, and you propose that introducing this tool into clinical practice as an adjunct to a simple Pap smear is going to improve the practice of medicine in some way. Okay. Show us how did that simple tool, just adding that to the Pap smear, improve the practice of medicine? However you define it, just give us a definition of what is your improvement and then prove it.

And it's got to be very simple because the more steps there are, the most post-hoc adjustments, the more statisticians there are in the room--and they all lie anyway, we know that--then nobody believes what anybody else is saying and the more adjustments there are. I think it has got to be very, very simple.

DR. DAVEY: Well, I guess just from looking at the

in vitro devices, though, if you don't have some sort of adjudication, you end up with a lot of results that people question. So I do think we need some of that.

I guess I would like to dichotomize the data two different ways. Suggest one negative versus low grade on up and the other is how does it pick up high grade in cancer lesions, and we can look at it both of those ways and ask manufacturers to divide the data both ways.

So we look at what is the improvement for high grade and cancers, but then we could also group all of the low grade, high grade, and cancers together in another way. I think that would be easy enough.

DR. LEVY: Well, for this particular study, where this one is an adjunct to the Pap smear, this might be the ideal two-armed study, where you have one arm that just gets Pap smear, routine, normal follow-up the way we currently practice medicine, and the other arm that has the adjunct, and then we can look at differences in those populations. For this indication, the two-armed study seems ideal, and that will resolve some of these issues for us in that it will be the way that these things are normally handled at the present time.

Now, we end up with the same problems further on down the line with other indications, but this would be an

ideal two-armed study.

DR. DAVEY: But what are you going to have for your follow-up and for your end point? Are you going to have to follow-up patients for a couple of years then or what? Because it seems like it would take a long time to get--

DR. LEVY: Oh, I think these studies will take a long time. As I said before, I don't think one, single Pap smear is an adequate screen for anybody, and I think we have already documented that. So, given what Dr. Schiffman has said as far as lesions coming and going and weeks at a time, rather than waiting two years and say we are going to repeat a Pap smear every year, what we may elect to do is--or the manufacturers might elect to do is pick high-risk populations, sexually active younger women who are not monogamous. They may have a list of criteria for those patients so that they can get more information more quickly, and they may elect to do Pap smears at six months rather than at a year. But I think we need at least two points in time and perhaps they would choose three in order for this two-armed study to work properly.

DR. O'LEARY: We are confusing two issues. The one issue is sort of the way we think that medicine should be practiced, and that, when we talk about the need for

multiple Pap smears and so forth, that is one issue.

But the device issue, it seems to me, is a slightly, which is the issue that FDA needs to deal with, is a slightly different issue in which the Pap smear is a test, a single test, a point in time right now, and we have a second thing that will be done to change that test, the Pap smear plus the "X" probe or device "X" and how we evaluate that.

I think that, both from the standpoint of getting a study design that is analyzable, as well as a study size that is feasible to most of the people bringing in a device, we need to focus on this single point in time. I think if we do other than that, we are going to, again, start to put--we are addressing not the FDA issue, but a practice of medicine issue, and I think it's a problem.

CHAIRMAN EGLINTON: Dr. Yin?

DR. YIN: I would like to echo Dr. Eglinton's point. I think it is very important if the company comes in and they say that I have this device to be used with Pap smear, then Dr. Eglinton's question is, "What is the added value?" And that is clinical utility. That is very important to the public, and to FDA, and to the clinicians. So that is the first question. So we need that answered.

Once they answer that question, then I am going to

ask the panel, based on this added value, what should be the end point that we are looking for that would direct us that, indeed, there is this added value. So I would like to see that addressed, and then you can say, well, how long should the study be in order to get us the right end point, to answer the question of added value.

I would like to see the sequence of thoughts and then you can plan the study accordingly, otherwise we will be running around all different directions, and then at the end we are still arguing which way is better.

But can I just build on his point of view, I like that thought because that would direct us somewhere and that would give the company a guide of what we really want rather than look for this/look for that.

Would that make sense to all of you? I think that is what I am concluding from all of the discussion from this morning from all of you. That is what I am hearing.

CHAIRMAN EGLINTON: Thank you. We have two more comments. Dr. Schiffman and then Dr. Robinowitz.

DR. SCHIFFMAN: I agree with that. I think that the only thing of absolutely clear value is the detection of high-grade lesions and cancer, cancer for downstaging, and high-grade disease for prevention of precursors.

In Costa Rica our adjunctive studies, which were

in 10,000 women, were designed to provide those plots where you have percent of women referred with a given combination or single technique and percent of high grade and cancers detected.

I found that very satisfactory because I knew it was a definite value, detecting all of that high grade, where I don't know if detecting every low grade is of real value. I know that it gets too murky. And I know that percent referred to colposcopy is effectively a cost function. If it is compared in the same--it is a proxy of specificity, really, in most settings where disease is rare, but you want to, for costs, you want to refer the fewest number of people to colpo and you want to have the near 100 percent sensitivity for high grade and cancer.

If I could guarantee 100 percent sensitivity for high grade and cancer to every clinician with low referral to colposcopy, it would be a very satisfactory screen.

So we consider those to be hard cost benefit numbers that are easily assessed. All of the other stuff I said was how do you make sure you pick up all of your high-grade outcomes. But that is what I suggest as end points.

CHAIRMAN EGLINTON: Thank you.

Dr. Robinowitz?

DR. ROBINOWITZ: I just wanted to point out--the panel knows this, but for the audience--that the actual approval by the FDA of a device is documented in the package insert, not in advertising, but in the package insert. So that the ultimate user can refer to the package insert just as a physician would the PDR. And that is actually the summary of the design, the data that was used to support the approval.

DR. O'LEARY: And I think that brings up two points. One, is that cost-effectiveness is a very important utilization issue, but it's not something the FDA is permitted by statute to address.

The second is that the indications for use here are paramount, and I believe that it's quite reasonable for a manufacturer to come in with an indication for use, which says that this improves the detection of high-grade lesions and that they can come in and state that.

I also believe that a manufacturer should be able to come in with an indication for use that says this detects the improvement of low-grade lesions, as well as high-grade lesions, and come in with that indication for use, whether or not we think that is reasonable.

If it meets that and there is a reasonable group of people out there, not a lunatic fringe, that thinks that

detecting low-grade lesions is worth doing, then I think that is a reasonable indication of use.

And so what we are really saying is make sure that your data support the label indication of use and make sure that you are not going to be losing patients along the lines, along any of these studies, which have high-grade lesions.

That addresses the FDA need, which basically says you have to have a legitimate indication, a legitimate indication, and you have to have studies supporting that labeling, even if you or I wouldn't want to use it. I have moved to approve instruments for use that I don't think have a place in my laboratory, but which indeed meet the safety and efficacy requirements that statute prescribes.

CHAIRMAN EGLINTON: Dr. Yin?

DR. YIN: I think that is well said, and I want to again echo what Dr. Eglinton said is the added value. Because we do ask the company to demonstrate that there is clinical utility. There is no need to have something just nice being thrown out there. That is one question we always ask, what is the clinical utility. That is exactly what Gary has been saying--added value. And I like what you just said. If there is added value in your clinician's mind and that is useful, then we should allow it.

I just want to say another issue is that for the advertisement, if we designated that this device is a restricted device, FDA does have more say about the advertisement. But you want to be very careful because do you want to designate every device to be restricted, okay? But we do have more say over that.

CHAIRMAN EGLINTON: Dr. Solomon had--oh, Dr. Schiffman?

DR. SCHIFFMAN: You leave me confused as to why I am here. You could say everybody with blue eyes goes to colposcopy, and that would have additional sensitivity for the pick-up of high-grade disease.

Now, I am not saying you are saying that, but I am saying that, if you believe, like I do, that the early approval of the DNA diagnostics, for example, in vitro they had for the detection of papilloma virus, but no one knew what the detection of papilloma virus meant, so there was a whole flurry of people using that indication in a way that, not only had no business in your laboratory, but really didn't make sense.

I think that, if you want to do a guidance document, the guidance I didn't think that it was cast in stone. I thought the guidance was like what is the optimal thing. I think the optimal is to stick to biological

phenomena that can be measured with reliability, with some degree of we know what it means.

I do not believe that low-grade lesion, as finding more low-grade lesions is something that is well defined enough now to be a gold standard in a --

DR. O'LEARY: And, you know, I agree with you, but I think the guidance document isn't a guidance document for practice. It is a guidance document for a manufacturer submitting an application to the Food and Drug Administration. I think it comes down to meeting the labeled indication for use.

In the case of papilloma virus, I wasn't involved in that. I can be relatively dispassionate. If the indication was identification of papilloma virus and it identified papilloma virus correctly, then it met its indication for use.

The FDA is not in the business of regulating the practice of medicine. They are in the business of regulating the interstate, you know, the manufacture of medical devices for interstate distribution and use.

And so a matter of just not overstepping the bounds, I think we want to really aim at making sure it gets to where it needs to go, and high grade definitely needs to be done. I think it is a wonderful idea to have people

focus on high grade. I would like to encourage that, but I am not sure that the guidance document should push too strongly in that direction, although I tend to share your philosophy because I am not sure that the FDA can go that far.

DR. SCHIFFMAN: But are you guiding people into a quagmire of methodologic problems?

DR. SOLOMON: Can I suggest that, perhaps, following up Diane Davey had said, is that you collect data such that you will know what the outcome is in terms of LSIL, as well as HSIL and above, and that you also incorporate some sort of statement to indicate that, obviously, it's HSIL that is the clinically significant precursor to cancer.

CHAIRMAN EGLINTON: Dr. Davey had a comment and then Dr. Wright.

DR. DAVEY: I just want to agree. I think, although this is a guidance document, we have to be pretty strong on that or the manufacturers and the public may get the wrong idea about what we are trying to accomplish. That is all I wanted to say.

CHAIRMAN EGLINTON: Dr. Wright?

DR. WRIGHT: I am struck by the fact that the way in which you draft this guidance document has the potential

for changing clinical care practice in the United States. And I am surprised that, in developing a document, such as this, which is only to act as a guide to the development of clinical trials, you would want to have such a strong statement as far as clinical practice.

There are multiple guidelines, which are extant in the U.S., as far as how do we practice. Patients with low-grade SIL Pap smears and low-grade CIN is a recognized entity. American College of Obstetrics and Gynecology has practice guidelines, the American College of Family Practitioners have practice guidelines, and the National Institutes of Health has practice guidelines for low-grade disease. So it is an established entity. I do not think you should ignore it for developing a device.

If you only use high grade and cancer as your end points for this device, it will be clinically unacceptable to many clinicians practicing in the United States who do care about low-grade disease and whose patients care about low-grade disease, and that is a current practice in the United States.

CHAIRMAN EGLINTON: Thank you.

Dr. Yin?

DR. YIN: I would like to ask the question another way. If this is--I am not a clinician, so I am allowed to

ask this question for the clinician to answer. If we have a device that will be able to, like this one here is to determine the ASCUS and LSIL, if we can identify that and then the clinician may use that information and say that, well, this patient we'll need to follow-up and need not go for colposcopy or biopsy, would that be useful? I mean, that you can decrease the need for the biopsy or colposcopy, would that make sense to any one of you? I don't know.

For the mammographic area, we did say that a device that you may send less people for biopsy is very helpful. I don't know about this part here. Now, if that is useful, then maybe we can use the indications slightly differently. I'm merely asking the clinician.

DR. LEVY: Colposcopy and biopsy is expensive, and with the number of ASCUS Pap smears and low-grade lesions that we are seeing, it is more and more common, I mean, our colpo clinics are backed up everywhere for that very reason. So that would be a very clinically useful outcome, yes.

CHAIRMAN EGLINTON: Yes. I can echo that. In point of fact, I have given up doing post-partum Pap smears because they all come back ASCUS. So I just don't do them. I leave the lady on her normal annual schedule and, you know, "When was your last Pap smear?"

"It was September."

"Okay. Come back and see me in September." That is what I am telling women I see this week in post-partum visits. I just don't do them any more because they are all abnormal.

Go ahead.

DR. SOLOMON: I agree with everything that has been said. I think, perhaps, we are getting into a discussion of use as a triage. I don't see how an adjunct to the Pap smear can actually decrease the rate going to colposcopy. So if we are finished discussing Indication 1, perhaps it's--

DR. SCHIFFMAN: But we have to, the last part about significant decrease and specificity has to be done.

DR. SOLOMON: I am not sure we are finished. I was just trying to put off that discussion. I think it is very necessary and critical, but I am not sure it goes here with the first indication.

CHAIRMAN EGLINTON: Well, the hypothesis, this is a suggested hypothesis, but it might not really fit in a simple limited protocol. Is that what you are talking about, Mark? I mean, if we are trying to--

DR. SCHIFFMAN: Just I agree with Dr. Hirsch. You just should put some confidence intervals on the change in specificity because there will be a decrease in specificity.

The question is, is it acceptable? Is it affordable? Is it reasonable for the amount of gain in what we are saying is LSIL and HSIL, hopefully, separately.

You will get a sensitivity gain. The question is do you have only a reasonable decrease in specificity? It is a value judgment that should be done with confidence intervals.

CHAIRMAN EGLINTON: Dr. Diamond?

DR. DIAMOND: For the purposes of this study, not necessarily for subsequent clinical practice, in order to show the added value of device "X," I think it is going to be necessary that each of the patients, even those that come up with negative Pap smears, initially, and device "X" studies would show "normal," that those patients have colposcopy or biopsy or some other end point to know were both of them right or what percentage of the patients are each of those entities going to be wrong for.

And that would be the case for patients to come up with normal Pap smear and abnormal reading from device "X" or vice versa or both being abnormal.

DR. O'LEARY: I am sorry. Two comments have been made, neither of which is obvious to me.

The first comment was Dr. Schiffman's about necessary decrease in specificity. There isn't necessarily

a decrease in specificity. There may be a tolerable decrease in specificity, but indeed you can use--if they are detecting things that are sort of mathematically orthoganol but biologically equivalent, then you don't necessarily have to decrease specificity. That is the first thing.

And then the question of specificity for what is what our whole discussion was about, and we probably said everything we can.

DR. SCHIFFMAN: It just never seemed--

DR. O'LEARY: It's unusual.

DR. SCHIFFMAN: Yes, very.

DR. O'LEARY: But it is mathematically possible.

The second thing is that the question of the negatives and I guess it is not obvious to me why that study needs to be done that way for this indication for use. For some of the other indications for use, that would be obvious, but in this case it is not obvious to me.

DR. DIAMOND: If you have a Pap smear that is normal and a device "X" study which is abnormal, how do you know whether--

DR. O'LEARY: Oh, abnormal. Okay. Those have to be colpo'd, yes.

DR. DIAMOND: And the other question is how often are you going to have a Pap smear which is normal and a

device "X" which is normal? Which is, in fact, the patient who has an abnormal cervical pathology?

DR. DAVEY: Yes. We won't know that.

DR. DIAMOND: Unless you--

DR. DAVEY: Follow-up.

DR. DIAMOND: Well, follow-up is one thing or the other thing is to refer all of those patients to colposcopy or whatever the next order of assessment is going to be.

DR. O'LEARY: Right. You won't know, but the part that you are comparing is against Pap smear normal, which is current standard of practice. So that is information I would like to have, but I am not sure that it is necessary for establishing this indication for use.

DR. DIAMOND: I am not sure that is correct; that it's added value to Pap smear.

The question is will this give us information which we wouldn't have gotten from the Pap smear, and the other point is how often will this device be normal and the Pap smear still be abnormal, the cervical pathology still be abnormal.

There have been many comments around the table that you need to have, as a general rule, multiple Pap smears in order to find out whether or not there is truly pathology. But in clinical practice, that is not what is

done. And so if you don't have the true incidence of abnormality, you are going to miss how much additional benefit may have been obtained from this device or how often this device may also miss a true abnormal.

CHAIRMAN EGLINTON: Dr. Schiffman and then we have two from the audience who might help us.

DR. SCHIFFMAN: You take the Pap smear positives out. Now you have a bunch of Pap smear negatives. Now, a really bad additional test would pick up additional positives only at the same rate as they exist randomly in the--that was my "blue eye" example.

So I always take a random sample of the negative/negatives because I want to know that the rate of additional positive pick-ups exceeds just the rate of misses randomly.

DR. O'LEARY: No, that is true, but that is already addressed by this question significant decrease in specificity.

DR. SCHIFFMAN: Well, what does significant mean? If you have a very large study, it will be statistically significant. It can be only 1 percent or 2 percent, and it can still be significant.l

DR. O'LEARY: I guess I was sort of mentally going along the line that Dr. Hirsch referred to yesterday. You

have to have a tolerance interval for that. Maybe that is really the question that ought to be framed is what constitutes a significant decrease in specificity.

MR. POLLARD: Just one minor point of clarification. That was written in there not to mean statistically significant, but a clinically meaningful significance.

DR. SCHIFFMAN: That is what I was saying. That is what I meant.

MR. POLLARD: I think you still have that question, what is a clinically meaningful decrease in specificity, but that is what the purpose was there.

CHAIRMAN EGLINTON: We have two people from the audience are trying to help us, and we could use some help. Could you, please, sir and ma'am, come up.

DR. LONKY: I am Dr. Lonky, Stewart Lonky, from the Trylon Corporation.

Having spoken yesterday, maybe I can clarify this point.

There are really two points at issue here. No. 1, is whether or not the negative/negatives; that is, Pap negative/device negative, should be sampled. If you don't sample them, then the only people who will be sampled are people who either have a positive Pap or a positive device.

That means the Pap plus device will always have a sensitivity of 100 percent.

So now, if you have a multitude of devices coming down the line, you can't tell one from the other because they are all going to say they are 100 percent sensitive.

The reason for doing what Dr. Schiffman had recommended, in the least, which is taking every third or every fourth negative/negative and putting them through the metric is what I recommended yesterday--well, what I recommended was doing every one--that any device should go through that study first so it establishes how it samples the universe.

Those studies would be used comparing one device to the next device--how it performs in that metric. Because after that all of the studies that you are going to do, Pap plus device, will have 100 percent sensitivity.

Plus, if you do Pap plus device and only they get colposcoped, then you get to the second issue; how do you calculate a specificity? You can't because Pap negative/device negative that cell will have zero, and so your specificity will be zero.

So you really have to address that issue, and my recommendation is that the guidelines state that performance in the real universe, as tedious as some of you may think

that is, we have done it, and it is somewhat tedious, and it is not all that terribly expensive, particularly for the companies that are really trying to see what--and for FDA--to see what they are really adding to the party, as Dr. Schiffman had said.

The important thing is that you can find 100 percent Pap plus device in a study of 3,000 patients and they had only two patients with low-grade disease. So you would have a higher sensitivity perhaps.

Thank you.

MS. CANFELL: Hi. Karen Canfell from Polartechnics.

I would just like to comment on that. What we are trying to do here is demonstrate an increase in sensitivity overall when compared to the Pap smear alone. So we are looking at the increased rate of pick-up, bearing in mind that this is in a general population. So any trials we are talking about, especially if we are looking at high-grade lesion pick-up, are going to be pretty large trials.

And what we are talking about, if we are talking about getting an ultimate diagnosis for all of these patients, is referring on a large number on to colposcopy and histology maybe in the range, say, around 10,000 patients.

And what we are suggesting is that we follow a kind of protocol that has been talked about here, where we refer on those patients who test positive with either the new device or the Pap test, and that we also refer on a proportion of patients who test negative with both devices, which will give us an idea of what is happening in that negative group. And that will still allow us to make that estimate of specificity that we need.

Thank you.

CHAIRMAN EGLINTON: Dr. Hirsch?

DR. HIRSCH: Yes, I agree with that. But from a statistical point of view, when you are taking a sample of the double negatives to estimate the false negative rate, there are, hopefully, so few false negatives in that group we need to recognize that that estimate is made with a lot of imprecision, and that can fall on either side of the fence. They can either overestimate the effect of the bias or underestimate the effect of the bias.

So if it is possible to, rather than take a one-tenth/one-quarter sample of the double negatives, if it is possible to get that information on them all, that is a safer thing I think for the sponsor of a device to do.

CHAIRMAN EGLINTON: It is going to be much more statistically defensible. The confidence interval issue

comes up if you only sample every fourth or every fifth or tenth or something. The confidence interval just keeps getting wider, and wider, and wider. And you may shoot yourself in the foot because you find ten really bad ones in those double negatives.

Dr. Davey?

DR. DAVEY: So are we going to suggest then that that be done? Because the other thing that was mentioned was if you follow patients over time you could maybe accomplish some of the same thing. I mean, we could either be pretty stringent in making a recommendation that another test be done on all negative patients like colposcopy or we could recommend that that approach or follow-up Paps or something else.

So, I guess, the question I still have is are we going to be pretty definitive in recommending that or are we going to give a couple of options to manufacturers?

DR. SOLOMON: The problem with follow-up is that you never know whether the patient was infected in the early--

DR. DAVEY: Exactly.

DR. SOLOMON: And I think that that adds all sorts of complications.

DR. DAVEY: So should we start taking notes as to

some consensus? I guess, that is what I am wondering. It sounds like looking at the negatives is one thing and the other thing is looking at the data both for low grade on up and high grade on up and, basically, recommending that manufacturers collect both of those pieces of data.

CHAIRMAN EGLINTON: Yes. I think the point Dr. Hirsch made there was don't throw any data away.

DR. LEVY: Yes. And perhaps what we really need to do is collect our Pap smear or our Pap smear plus device and our colposcopy all three or all simultaneously. Because based on what Dr. Schiffman said yesterday, even in the interval of six weeks, by the time we get a Pap smear back and bring somebody back simply for colposcopy, they could be shedding at one time and not shedding at another time, and that is not a Pap smear problem. That is a sampling problem.

So perhaps what we need to do is set up a pattern in which we do the Pap smear and colposcopy or the Pap smear, device, and colposcopy at the same visit, at the same time. That is actually less expensive, and biopsy only if there is something abnormal at the colposcopy.

CHAIRMAN EGLINTON: And the colposcopy could be done by a different operator who didn't do the Pap smear or the device or whatever.

Dr. Hirsch?

DR. HIRSCH: Yes. I'd like to kind of make a general recommendation, and that is, instead of trying to include in the guidance document the perfect protocol, I think that we have to recognize that there is no such thing, and there are going to be problems.

Maybe the guidance document would serve better if it listed the kinds of concerns that you have in these kinds of studies; concerns with resolution of discrepancy, concerns with taking a subsample of the double negatives, and then say that these are things that the FDA is going to have on their mind as they review protocols, and they review PMA as well, and not try to tell them how to answer it.

If I were a sponsor submitting a protocol, I may have a sound argument that this particular course is the least of all the evils for study design, and if I can make that point, I would think that the FDA should agree with me that I have done the best that I could on that particular study.

DR. SOLOMON: I'd just like to get back to one other question that had been raised, and that was whether we needed a two-armed trial. I, personally, am not convinced of the need for that, and I just wanted to be sure that you were comfortable with not requiring or needing a two-armed

trial with this design.

DR. DAVEY: Well, I'm more comfortable now if we have a study of the double negatives. I was very concerned about just using one Pap smear alone. I mean, I can understand what people are saying as added value, but then you end up with not knowing, and I have just seen this in other studies, and I think we need to have something on that.

I did want to make a comment, though, about the Pap at the time of colposcopy. At least in our institution and multiple other institutions, there have been a few published studies on this. The Paps done at the time of colposcopy are often less sensitive, and we just have to remember this and address this. And I have a big concern about the Pap looking very bad. I don't know what the reasons are for that, but that's-=-

DR. SOLOMON: I think that is different. That is colposcopy following an abnormal Pap.

DR. DAVEY: Right.

DR. SOLOMON: And I think what you were saying is the first Pap, and the device, and the colposcopy.

DR. DAVEY: Yes, I know what you are saying. But we have to make sure that the patients then haven't had a Pap a month ago or so or that the entrance is very correct

into the study. Because if they have had a Pap a month or two ago and then they are going to have colposcopy, Pap again, that is going to be a problem.

DR. LEVY: Well, the other issue with Paps after colposcopy is often they have been treated with acetic acid prior to and the cervix has been dried and a bunch of other things have happened before they get their Pap smear. So, clinically, we even know that that is a bad sample when we take it because there are very few cells on the Pap.

DR. SOLOMON: One comment, which I think was mentioned several times yesterday was that the interval between the Pap and device to colposcopy, if you are not doing it all at the same time, that an interval of four weeks was unrealistic. So I guess I would be interested to hear--

DR. DIAMOND: But that could be very different if you knew that that was going to be the protocol and that you would, rather than waiting for an abnormal Pap to come back, and then having to wait two weeks for it to come back and then reschedule the patient, if you just schedule the patients for all of them simultaneously, I think that might be a very different issue.

CHAIRMAN EGLINTON: I am not sure that answered your question.

I agree, four weeks doesn't work in clinical practice. You don't get Pap smears back and get time to schedule a lady for colposcopy in routine clinical practice.

DR. LEVY: But it works if we are going to colposcope everybody.

CHAIRMAN EGLINTON: Right. If you are going to do everybody, then it's going to--

DR. LEVY: And it's part of the study protocol, then you just schedule them in four weeks.

DR. SOLOMON: But colping everybody is one option versus colping a percentage of the double negative patients was another option we considered.

DR. LEVY: That won't work.

DR. SOLOMON: I am just trying to cover the bases in the event that a manufacturer wanted to use the approach of colping a percentage of the double negatives, plus everyone who was positive by either Pap or the device.

I would just like to hear what is a reasonable interval.

CHAIRMAN EGLINTON: Dr. Burke?

DR. BURKE: Before we address the reasonable interval, we get back to one of the statements we made about the purpose of this as an adjunct, and we are talking about screening general population.

Now, as soon as you add colposcopy to it, you are not going to screen general population. You are going to now have patients who are willing to accept a fee, and that comes down to our indigent population, and not our upper-income population, who are going to submit.

Whereas, most patients if you say, "I have a light that I have to shine on your cervix, and it is a simple test," they will allow you to do that, and you could get a better sample of what we are talking about. But as soon as you add the idea that they are going to be submitted to a biopsy or possible biopsy, you are going to immediately create a bias to what we are trying to screen.

If we are screening general population, then you have got to just use the two tests and somehow or another figure out something to do about the negative/negatives.

And, again, I would reiterate we couldn't handle having it done within four weeks, unless you did immediate colposcopy and, again, we come back to the same point.

DR. DIAMOND: But the purpose of the study is not to screen the general population. The purpose of the study is to evaluate the efficacy of the device in providing an added value.

DR. HARVEY: Please use the mike.

DR. DAVEY: I don't think you can get enough

numbers by just doing a general population. I think you are going to have to do these studies on a relatively high-risk population if you want to find statistically improved detection of high-grade lesions and cancer.

So although the ultimate goal may be to do it on the general population in the studies, you are going to have to try to get enough patients that might have a high-grade lesion.

CHAIRMAN EGLINTON: Dr. O'Leary?

DR. O'LEARY: Two things. One is, in dealing with the four weeks issue, might I suggest that it be finessed simply by stating that the interval should be kept as short as possible and that four weeks would be ideal or less would be ideal, something on that order, but language that is a little bit weaker on that side.

Secondly, to maybe ask Dr. Hirsch and the FDA to work on the statistical side to incorporate some of the statistical comments and study trial design generalities into the document that he discussed yesterday.

I think FDA's clinical trials guys, quite frankly, are probably better than any of the rest of us, at least, sitting around the table on that, and I think we have brought forth a lot of the relevant issues, and that working together those details of how clinical trial should be

designed are probably beyond what the guidance document should show. But those general considerations that have been brought forth should get in there, and the way to do that is off-line.

CHAIRMAN EGLINTON: Yes, ma'am?

MS. CANFELL: Karen Canfell from Polartechnics.

I would just like to reinforce the point that was made earlier, that we believe it is very important to test these devices on the test bed in which they are ultimately used--and this application we are talking about general screening in a primary care facility--and to structure a study so that you have the kind of quality colposcopy that we would need may affect that scenario.

We have done the numbers for this kind of study and agree that we are talking about a lot of subjects to get the data on a general screening population. We think we need around about 200 patients with high-grade SIL, and that works out to 10,000 patients or maybe even more in a general screening population.

Now, that is possible to do as a study, but it's certainly not possible if all of those patients have to undergo colposcopy. That is something that is simply not financially viable for a sponsored study like this one.

Thank you.

CHAIRMAN EGLINTON: Dr. Lonky?

DR. LONKY: Stewart Lonky from Trylon Corporation.

I just wanted to echo one response to the statement that was made, and that is, having the experience of having done some 5,000--nearly 5,000--patients in studies in which everyone got colposcoped, we have not yet had to pay patients or had any problems even in a managed care organization like Kaiser Permanente where we have patients understand the rules of the study.

You do get one selection bias and that is people who like to be in studies. But they tend to be people who have better medical care and not worse medical care.

CHAIRMAN EGLINTON: Remember, this is just adjunct. We are talking about just the indication as adjunct. We haven't talked about appropriate sequence of testing with different detection diagnostic methods; Pap smear, the device, colposcopy, biopsy, and so forth.

MR. POLLARD: Dr. Eglinton, I just wanted to make sure that the panel had not overlooked the comments that came to us from the American Society for Colposcopy and Cervical Pathology. This is in a letter that should be in your folder from a Dr. Cox.

There were some comments, actually, with regard to the feasibility study that had to do with the sequencing of

tests. That was, actually, on the first page.

DR. HARVEY: If anybody on the panel needs a copy, I can give it to them. You should have it, though.

MR. POLLARD: It's like a four-page letter there, and I think there are probably some valuable comments there, including some on sequence, although they are directed to the feasibility aspect.

CHAIRMAN EGLINTON: Has everybody found this?

The point I think Colin is looking at is paragraph A, subparagraph 1, page 7, line four from bottom. "The statement outlining the order seems to be reversed from the order we would expect if the intent is to determine whether the device traumatizes the cervix. If the in vivo detection device is patient-contacting, the colposcopy should be done first followed by the IVD, followed by repeating the colposcopy. If the device is used first, trauma from speculum, tampon use, et cetera, could not be documented to be already..." and I think everybody can follow the logic there.

I am not sure that we can resolve it. We certainly can't be proposing that somebody is going to wash the cervix with acetic acid and then apply this device unless somebody has told us that it sees the same whether the cervix has been washed or not.

DR. DAVEY: I thought he addressed the acetic acid. They address that later on. And then they said that you wouldn't use acetic acid, later on in their letter, that you wouldn't do the colposcopy with the acetic acid until afterwards.

CHAIRMAN EGLINTON: You would look for micro-trauma first and then do the--

These are obvious questions that are going to come up with a manufacturer presents the PMA. They will have to answer the challenge.

DR. DAVEY: Offhand, most of the suggestions seemed reasonable to me, but I think we need a Gyn oncologist to look at it.

CHAIRMAN EGLINTON: And then some of this would be from pilot or feasibility study just to see is there anything that you can see; is there any effect that you can detect, but keeping in mind, if it is something that doesn't happen very often, you have to do 10,000 of them to see if it happens.

Dr. Yin?

DR. YIN: Again, I'd like to share with you what we are doing in the mammographic area is screening. Right now we use the film, you know, to look at the film and you decide whether there is suspicious lesion or not. It is

just like you do your Pap smear to see if it is suspicious.

Now the companies what they want to do is to do a digital mammographic study. That means filmless. So, in reality, you would expect that they should be reasonably comparable, right? Should be, one is with film and one is without film. Except the one that they are going to use--the digital one--they are saying that it may be more sensitive, but just try to do a study with a regular screen versus something that may be a little bit better.

So we are designing study for that study, and it is a big study, I mean, if you are going to just have two comparative study. So I am sharing that with you because this is very similar to the mammographic study that we are talking about, very similar. So do not underestimate the numbers that you may require.

But in that particular study, what we did was we designed agreement study because we did bring all of the companies in to work on that together, and then we also, if they are going to claim that digital mammography is better, then we design another study allowing them to make that claim.

So they could say that I am just as good as film or we are better and, again, you are very aware that in order to catch the breast cancer versus those general

screen, that is a small number, just like what you have here in the cervical cancer if we are talking about a general screen, and that is the number four study.

CHAIRMAN EGLINTON: Does anybody care to comment further about the order or the sequence of testing? There will just be some words included suggesting that there be considerations--in other words, we are not writing somebody's protocol for them here. They are going to have to justify the sequence that they used when they come back with the PMA.

We are not going to write word-for-word the entire protocol here. This is just rough guidance. And when you bring a PMA forward, you are going to have to justify why you chose to do things in the order that you did; whether it is feasibility or clinical study.

Professor Coppleson?

DR. COPPLESON: To obtain the optimal results with the in vivo devices, the epithelium should be least damaged when the test is done.

A substudy would show, I believe, that the in vivo devices do not cause a great deal of damage to the epithelium. That is our experience in the thousands of cases we have done.

The Pap smear's purpose is to exfoliate cells from

the cervix. So we will take the Pap smear, it does two things; it will remove a lot of the key cells from the ectocervix and the lower endocervix and frequently, particularly if a cytobrush is taken, you will have a lot of blood coming around.

So the sequence, I would suggest, should be the in vivo test first, then if colposcopy is done, the colposcopy second--because, again, if you have used a cytobrush, you often get quite a lot of bleeding, which interferes with the colposcopic assessment--and, third, and I admit it is after acetic acid that the Pap smear is done. But I am presuming here that there has been another Pap smear done, particularly in the adjunctive test, and that the Pap smear is ASCUS and above. The other Pap smear has been done before.

And a substudy can almost be done comparing Pap smears done after acetic acid versus Pap smears not. Another substudy is that the probe could be then put into a liquid cytology medium, see what cells have been removed by the probe, and then that is compared with the smear that is done after the probe to see where a sufficient or too many cells have been removed by the probe.

But the sequence, I would suggest, to give the in vivo methods a proper trial, is that they should be

performed first.

CHAIRMAN EGLINTON: Do you put a speculum in?

DR. COPPLESON: Yes, the speculum does go.

CHAIRMAN EGLINTON: Dr. O'Leary?

DR. O'LEARY: There are two things, one of which I just thought of. I agree with you. I don't think we need to specify the order. It is just that that ordering, whatever is done in the trial, needs to be showing up in the documentation for use because that is the combination that would be used in practice.

I think, though, that it is important to get a statement in here to the effect of the nature of the Pap smear that is taken because we do have thin preps coming out, and it's entirely possible that there will be a difference in combination and effectiveness in use with thin preps versus "conventional" prep, and that should be specified very carefully and should, ultimately, be in the use document, at least until we know that there is equivalence.

CHAIRMAN EGLINTON: And there may be a necessity for some feasibility studies up front first. As Professor Coppleson says, if you rub this thing all over the cervix, maybe you ought to see what you have exfoliated versus doing the Pap smear first without the brush and then this and see

what you exfoliated, what you have scraped off with the spatula.

How many centuries had you planned to do all of this testing? Is this for the 22nd Century?

[Laughter.]

DR. DAVEY: Okay. So we're going to recommend that we can't really say the order now until the feasibility studies are done showing what effect. But I think we need to be pretty clear that we are concerned about the Pap, that it not be done after--that the initial Pap not be done after acetic acid in this adjunctive study, and that the nature of the Pap smear in any of the study needs to be specified, but we don't need to require a certain type versus the other; is that what you are saying?

DR. O'LEARY: Right. Because we are going to be looking at the effectiveness of the combination.

So even if the ordering were to make the Pap smear pick up worse, if the combination was demonstrably better, then that would be okay. And so I think it is just a matter of making sure that the net system performance is improved.

DR. SOLOMON: But if you are comparing the net system against the cytology alone, to me, that does make a difference.

DR. O'LEARY: They are going to have to be very

careful in study design. That is right. That would require them to go to a two-armed study, in that case, and have cytology alone and demonstrate improvement over a two-armed study. In that case, you are really forcing it into a two-armed study.

CHAIRMAN EGLINTON: Dr. Schiffman?

DR. SCHIFFMAN: Very briefly. In bringing the new technologies into the natural history studies, there have been many, and it seems in every case these little details determine the winner. Because you can make subtle adjustments to expert review versus indifferent performance, and everything has to be done sort of with a proponent backing it. You really want someone pro-cytology doing the cytology and pro-visualization doing the visualization.

So I favor asking for documentation of the personnel, their training, their whatever, on every aspect, even the so-called standard or reference techniques.

CHAIRMAN EGLINTON: We need to kind of wrap up here.

Michael?

DR. DIAMOND: Another issue, very briefly, that we have not touched upon.

I am not sure how big some of these devices will be. But as the devices get larger, their ability to go down

into the endocervix may be reduced, and in those patients in whom the transformation zone has gone into the endocervix, the device may not be appropriate, even if it would have worked if the transformation zone was out on the ectocervix.

So there probably needs to be some thought by the manufacturer as to where, in what patients, or at what location of the transformation zone will their device be appropriate, will that make a difference.

CHAIRMAN EGLINTON: In that regard, the parity of the patients may play a role as well. I mean, if she is older or has had more children, the transformation zone is receded further up, but maybe the external is more patent and it's easier to look up higher.

DR. LEVY: I think what we will need for that is clinical data on data sheets and collection sheets that talk about previous cryosurgeries--the thing that is going to affect it more than anything--menopausal status. There are several issues that will affect that, and I think that having that information included on a data sheet would be the most appropriate way to look at that.

DR. SOLOMON: Just to let you know, actually, all of those items are already discussed very briefly. Perhaps we should expound on them in page 9 of the document. That is sort of an overarching discussion, regardless of the

proposed design. It really affects patient population selection for any of the intended uses.

CHAIRMAN EGLINTON: Does anyone have any further comment, other than what we have already discussed on feasibility versus efficacy? We have talked a lot about some of these things are obviously going to have to be done up front, feasibility first before a clinical efficacy study. Does anyone have anything further to add?

DR. SCHIFFMAN: For No. 1?

CHAIRMAN EGLINTON: Yes, for No. 1, Indication No. 1. I hope nobody made reservations to leave the local area this week.

[Laughter.]

DR. SCHIFFMAN: Have we gotten rid of the word ASCUS on page 11 at the top?

CHAIRMAN EGLINTON: That is Indication No. 2.

DR. DAVEY: No.

CHAIRMAN EGLINTON: Oh, I'm sorry. Okay, in the first line.

DR. DAVEY: Yes, I think we should strike that.

DR. SOLOMON: We can rid of ASCUS, Mark, if you can answer this question: When you are comparing a device plus Pap versus a Pap as an indication for a woman to go to colposcopy, what level of cytologic abnormality should you

use?

DR. SCHIFFMAN: Well, we just recalculate based on each cut point ASCUS and above, LSI and above, whatever. It just gives you a different sense of performance data. I just think ASCUS can never be mentioned as a gold standard on the disease side of things.

DR. SOLOMON: This isn't, I don't think, a gold standard. This is to do just that, to determine what, if you use ASCUS as a cut point, what happens in terms of detection of HSIL.

DR. SCHIFFMAN: Oh, I thought those were three disease categories, not three test categories.

DR. SOLOMON: No. This is doing just what you want to do.

CHAIRMAN EGLINTON: I think this is Dr. Hirsch's point again. Don't throw away any data.

DR. SCHIFFMAN: I thought it was being mentioned as, like the way I don't like the idea of finding LSIL, true LSIL. There is certainly no true--

DR. SOLOMON: This is not to find. This is as a trigger.

DR. SCHIFFMAN: Okay. Sorry.

DR. SOLOMON: So you are happy.

DR. SCHIFFMAN: Yes.

DR. DAVEY: But I am still confused then. We are going to say the Pap, we are going to use different Pap cut-offs, but the machine cut-off won't have--that is just anything abnormal versus negative. Because there is no ASCUS for the cervix, there is no ASCUS for the machine, so you were just talking about purely on the Pap alone, and then we are going to have the two cut-offs, though, for detection of low grade on up and detection of high grade on up.

DR. SOLOMON: As the end points.

DR. DAVEY: In terms of the end point.

DR. SOLOMON: Yes.

DR. DAVEY: Right.

DR. SOLOMON: But the device conceivably could have some sort of output that would grade, it wouldn't necessarily be normal/abnormal.

DR. DAVEY: Okay. I see.

DR. SOLOMON: The device might say yellow, red, green or something.

DR. DAVEY: Well, I agree with the different divisions for the Pap, but then for anything else it has got to be a different--

CHAIRMAN EGLINTON: It depends on what the instrument gives you for an output. If it gives you a red

light or a green light and that is it, but if it gives you 13 different lights, you need to "salami slice"; cut your data just as it shows up.

DR. O'LEARY: Can I ask max from Clinical Laboratory Devices a question on this? Because as we went through the issue of dealing with the rescreeners, it seemed to me it was pretty important to the staff of the Division of Clinical Laboratory Devices that we do no worse on "ASCUS up" as a diagnostic end point, if you want to call it that, for cytology than if we were to go forward in a prospective fashion to consider licensing for prescreening or for initial screening.

We need to be getting some kind of consistency, if possible, between the clinical laboratory devices arena and this arena. How do you suppose the staff of Clinical Laboratory Devices would look at this question of ASCUS in the screening category?

DR. ROBINOWITZ: I think the important thing is that whatever the study is it is clearly stated what the object was, what the inclusion/exclusion and all of that sort of thing is because in comparing the various protocols manufacturers come in, it is a case-by-case decision. And I think the, as someone stated, there are people who may want to know ASCUS, LSIL, HSIL, even though, as Dr. Schiffman

said, the biology is such that there is a distinct difference between high grade and low grade as far as the pathobiology.

But one of the things I was thinking about is the lack of agreement between pathologists on what is high grade and what is low grade and sort of the shift in the criteria. So I think that is another factor.

But to summarize, I think that if a manufacturer wants to claim ASCUS, low grade, high grade as different cut points, I don't think we should or can or would want to not allow them to.

CHAIRMAN EGLINTON: Thank you.

Does anybody have anything, any other burning points to make on Indication No. 1?

Ms. Domecus?

MS. DOMECUS: One quick point. I am not sure where we ended up on the reference diagnosis question, but I heard several comments suggesting that there be repeat Pap smears, and I am not sure that that doesn't place an unfair disadvantage against experimental device if the control, if you will, is having repeat tests because it is increasing its opportunity to be correct or more correct and then the experimental device only gets one shot at it. It didn't seem like a fair comparison.

DR. SOLOMON: I think that fell by the wayside. That was when we were discussing the possibility of following patients, but I think that the consensus was that it would be preferable to either colpo everyone or to take to colpo a certain percentage of the negative/negative patients in lieu of a longitudinal type.

MS. DOMECUS: I wasn't sure where we ended up.

CHAIRMAN EGLINTON: Dr. Davey?

DR. DAVEY: Just a couple of points of clarification on page 10. We say, "Once the results of the Pap are received, if either the Pap or the device is positive," when we are talking about Pap we mean ASCUS on up, right, for positive?

DR. SOLOMON: Or the study design could be just everybody gets colpo'd.

DR. DAVEY: Oh, yes. Okay. That is assuming that we don't colpo 100 percent, right? But that is what we are considering. I just want to make sure that we know what we are saying is a positive path, and then we are going to add something about adjudicated review of biopsies or something like that at some point or recommend that. That was pretty well agreed on.

DR. SOLOMON: I think we need to do that.

DR. DAVEY: Okay. I am just going to make some of

these notes then.

DR. O'LEARY: Excuse me. Maybe somebody can clarify what we mean by adjudicated because I am concerned about the multiple comparison problem.

Simultaneous consensus and advance is one thing. Discrepancy resolution is quite another. The former doesn't introduce any statistical bias. The latter can introduce enormous amounts of bias depending on the nature of the discrepancy resolution.

DR. DAVEY: [Dr. Davey responded, but not speak into mike and was, therefore, inaudible.]

DR. O'LEARY: Okay. So you are looking at consensus diagnosis as the initial rather than a discrepancy resolution.

DR. DIAMOND: I would prefer that, but--

DR. O'LEARY: That one I mean is statistically clean.

CHAIRMAN EGLINTON: Okay. Are we getting close to the end of Indication No. 1 here? There will be no lunch. There will be no bathroom breaks until we get to the end of Question No. 1.

[Laughter.]

CHAIRMAN EGLINTON: There will be more time after lunch because we have to go through the same process for the

three remaining indications and then we have more questions beyond.

So is everybody reasonably content with what we have added to Indication No. 1 in terms of the guidance document--editing for Indication No. 1 adjunct?

Does anyone have any more comments?

[No response.]

CHAIRMAN EGLINTON: So we will be back here in one hour.

[Whereupon, at 12:17 p.m., the proceedings were adjourned to reconvene at 1:17 p.m. the same day.]

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A F T E R N O O N S E S S I O N

1:10 p.m.

CHAIRMAN EGLINTON: Let's go ahead and continue.

The format for this afternoon will be a little bit different in that we will try to forge through and answer our questions for each of our indications, all of the other discussion points here. And then when we finish, we will solicit comments and further assistance for our work from the audience. Otherwise we will still be here doing this by the weekend.

CHAIRMAN EGLINTON: Indications for Use No. 2. Perhaps we already agreed that we would cross out the word ASCUS, and this would be Indication for Use 2 is triage on page 11 of the draft. Does that sit well with people? Indication for Use 2 is triage. Triage, just generic triage, regardless of what you are triaging for.

What are the appropriate study subject inclusion and exclusion criteria? There are a couple of suggestions here: Description of patient population, Inclusion: Women with ASCUS or worse than ASCUS within the last four weeks. Exclusion criteria: None?

I think we all agreed we want pregnancy is probably going to be a reasonable exclusion for any of this at this point, right?

DR. LEVY: I thought we had agreed that we would leave it in and just allow women to self-select based on the informed consent document. That way the companies can decide if they want to do that or not, but we shouldn't put it in as an exclusion.

DR. DAVEY: Yes. I also thought that it depended on the feasibility studies, too. Some of the other conditions may get excluded out, but we don't know enough about how the device acts with other conditions, and so the feasibility studies would need to be done first.

Were we going to say last eight weeks or are we going to keep it at last four weeks? That was one question, I guess. We were concerned about the time interval. Low-grade lesions may change, but four weeks may not be possible for every situation.

CHAIRMAN EGLINTON: We've been talking about four weeks doesn't work well for clinical practice, but within the framework of a study, maybe four weeks is reasonable.

DR. LEVY: If we're going to schedule everybody back for colposcopy anyway, then a routine four-week follow-up as part of the study protocol would work. If we are waiting on the results of the Pap smear to determine which people we colposcope and which people we don't and only some people come back, that would be a problem. So I

am not sure we want to specify four weeks and just let the companies know that we have some concern that if it's a longer period of time than that, that exposure to the virus or that we may not be looking at the same lesion that we saw earlier.

DR. DIAMOND: And particularly for this protocol where patients are being referred in after the fact based on the previously abnormal Pap smear. You may have large areas where you are having screening done and being referred in. And so I think that this protocol, in particular, I would like to see it more than four weeks, be eight weeks or maybe even twelve weeks, but something larger.

CHAIRMAN EGLINTON: I mean, can we just leave it as an expressed concern that the longer the time transpires between screen and next visit the more concern there is over biologic variability?

Dr. Solomon?

DR. SOLOMON: Because we have expanded this to be not just triage of ASCUS or LSIL but, in fact, we may be triaging which women will require LEEP, I think that we should, for inclusion criteria, just say women with an abnormal cytology.

DR. LEVY: Screening test.

DR. SOLOMON: Abnormal screening test.

DR. SCHIFFMAN: We found it useful in one of our triage studies to specify that the exclusion criteria with anyone who had an intervening something other Gyn event because people were being confused about that. So if somebody has had an ASCUS Pap smear but then gotten treatment, they are not--that is all. So it might be worth mentioning a current Pap that has not yet been evaluated.

DR. SOLOMON: I'd just like to say hysterectomy is not included here, and I would like to ask the clinicians if they feel there might be utility for this in a woman who has had a hysterectomy, but has an abnormality on cytology to help localize or indicate which women might need further--

MR. POLLARD: I would just like to point out that in a letter from the American Society for Colposcopy and Cervical Pathology they actually suggest that as an exclusion criteria. So we definitely would like to hear some discussion of that.

CHAIRMAN EGLINTON: Where are you reading?

MR. POLLARD: This is on page 2, down in the second half of the page where they talk about ASCUS triage study.

DR. LEVY: My recommendation is that since the American College of Ob/Gyn has recently come out and recommended that we not be screening people with

hysterectomy routinely with Paps, even, as long as they haven't had abnormal or cancerous conditions, it is much cleaner if we just use previous hysterectomy as an exclusion criteria. In the future, the companies may want to expand their indications. But for now I think that that makes more sense.

DR. SOLOMON: Of course, women who have a hysterectomy because of disease, obviously, are continued--

DR. LEVY: I think for any reason, at this point, we are looking at the cervix, and we should be looking at the cervix. The more we try to expand this--

CHAIRMAN EGLINTON: I think it's going to be harder for a company to put enough numbers in that box--

DR. LEVY: I do, too.

CHAIRMAN EGLINTON: --than a matrix if they have to include patients who have had hysterectomy. They are just not going to accumulate enough of them.

DR. O'LEARY: Minor point, but in this Indications for Use 2 and 3, I would like to suggest that, like in Indication 1, that the heading "Study Design" be changed to "Sample Study Design."

CHAIRMAN EGLINTON: Under "Investigation Plan" beneath "Hypothesis"--

DR. O'LEARY: Yes.

CHAIRMAN EGLINTON: --say this is a "Proposed" or "Sample Study Design."

DR. O'LEARY: Yes.

DR. DAVEY: Well, if we're--actually, a little bit before that, ASCUS cervices doesn't make sense to me and to the hypothesis. I think we need to change that unless someone can define what that is.

DR. SOLOMON: I don't think anyone wants to define that.

DR. DAVEY: So cervices from patients with abnormal screening tests. I don't know.

DR. LEVY: Just get rid of the word "cervices." We want to differentiate ASCUS from high-grade SIL and low-grade SIL.

DR. DAVEY: But we also can use it as the other triage thing. Remember we changed it, so it's not just a triage for ASCUS either.

DR. LEVY: Right. So let's make the hypothesis say triage; that the device can be used to triage patients into appropriate treatment categories.

DR. SOLOMON: I'd like to see the same end points as we used for Indication 1.

DR. DAVEY: Yes. So what is the hypothesis going to be so I can write something down here?

CHAIRMAN EGLINTON: The IVD can be used to triage patients into appropriate treatment arms or follow-up arms.

You don't triage cervices. You triage patients.

[Laughter.]

DR. DAVEY: Appropriate treatment or follow-up arms, right?

CHAIRMAN EGLINTON: Right.

DR. DAVEY: And the end points would be LoSIL plus and HiSIL plus detection?

DR. DIAMOND: And since we have separated out patients who have had hysterectomies from the ones that we are studying here, then to be able to make a claim in the future to be able to look at the vagina and identify abnormalities, that would be a whole separate study or whole separate evaluation process.

CHAIRMAN EGLINTON: Having survived these wars over several years, I think that is the only way to be fair.

DR. DIAMOND: Subtotal hysterectomies would be among those women that would be allowed to be included, however.

DR. SOLOMON: Yes, if you have a cervix.

CHAIRMAN EGLINTON: I guess we are not talking about hysterectomy. We are talking about trachelectomy. If the lady has a cervix, she can be in the study.

[Discussion between Dr. Eglinton and Dr. Solomon.]

CHAIRMAN EGLINTON: Dr. Solomon is saying can we agree at the start that for Indication 2 everything we said about Indication 1 applies and now we are looking for things to say that will differentiate between Indications 1 and 2.

DR. DAVEY: I would agree, in general. Can I just bring up one other? When we are talking about colposcopy and the biopsies, are we including curettage procedures or not or does that depend on the study design or should we not even bring that up?

DR. SOLOMON: I think that has got to depend on the individual study.

DR. DAVEY: One thing I would like to say, though, you know, we are talking about blinding the pathologist as to maybe, I don't know what we are saying, original diagnosis.

I do think that before the histologic biopsy is signed out that somebody needs to know how high the level of concern was on the Pap because it is standard practice in many institutions to do deeper cuts on a biopsy; if a high-grade lesion was suspected and it's not initially seen in the biopsy to do deeper cuts.

And so, in any of these designs we need to, although we want to have some blinding, we need to make sure

that the appropriate histologic exam is done.

DR. O'LEARY: If we do that, to avoid bias, I think the best way would be to specify multiple cuts at the very beginning. Otherwise you are going to have the same kind of bias that Dr. Hirsch was talking about.

DR. DIAMOND: That actually brings up a whole other issue, which is, so as not to compromise clinical care, should the evaluations for the study be done by a pathologist that is, No. 1, off-site and not the one that is going to be contributing to the care of the patient, and, No. 2, that could be the same for all of the centers in the study as opposed to having interindividual variations among pathologists at different institutions.

DR. DAVEY: Well, one thing we did want to have a consensus diagnosis, though.

DR. DIAMOND: But that could still be done by--

DR. DAVEY: Right.

DR. DIAMOND: --blind the pathologist at a distant site as opposed to the local pathologist who is contributing to care, particularly if you think it may lessen the quality of care that patient is going to get. I am not saying we should specify, but it is something to put in the protocol that the company should decide.

CHAIRMAN EGLINTON: We've looked at a lot of

slides depicting the statistical variation or, say, the interobserver differences in looking at Pap smears much less biopsies, and that would reduce a lot of variability if everything were read up front in one site.

DR. O'LEARY: It also seems to be required to eliminate the bias that you may have if you are sitting and evaluating a particular specimen and you are not seeing much on your biopsy, but you are seeing a clear high SIL or you are seeing something else. That won't be a problem at that level, but in the intermediate zones it is quite clear that you will push your diagnosis around. That will eliminate that problem.

DR. DAVEY: So what should we say; that the histologic assessment for any of these needs to--the final should occur by some independent panel or a consensus approach?

DR. SCHIFFMAN: Sometimes we have had great difficulty in having clinical centers agree to taking all of the pathology off-site, but they will agree to review off-site. So you are talking about the study diagnosis will be the review diagnosis done uniformly, as opposed to individual--

DR. DAVEY: I am sorry. What was the wording?

DR. SCHIFFMAN: I never can remember what I said.

[Laughter.]

DR. DAVEY: So the final histologic diagnosis would be--

DR. LEVY: The review diagnosis.

DR. SCHIFFMAN: The review diagnosis would be done uniformly off site.

CHAIRMAN EGLINTON: And that is the final study diagnosis.

DR. O'LEARY: And without reference to the initial diagnosis.

CHAIRMAN EGLINTON: Without reference to the cytology.

DR. SOLOMON: Well, the initial diagnosis is usually included in the algorithm to get to the--

DR. O'LEARY: But what I am saying is that we want to blind the reviewers to the diagnosis originally arrived at, at the sampling site.

CHAIRMAN EGLINTON: Because it's a study. It's not clinical practice, it's a study, and they should assume that each one of these specimens has some equal low risk or equal high risk, but they should all be treated the same.

DR. DAVEY: And that the histologic slides should have multiple levels done. I don't know if they will send them all off. That may be a problem. A lot of places will

not. In fact, we would not send all of our slides off-site or release our blocks and everything. We would send representative things.

DR. O'LEARY: Well, the company could have the review panel review on site. That may be the alternative. But the problem if we do multiples and then only send them off is that the submitting pathologist is going to keep the good one to support--the one that best buttresses the local diagnosis at home.

DR. SOLOMON: I think we're getting into too much detail here. I think we ought to just specify that we need some sort of review diagnosis.

DR. SCHIFFMAN: Can I ask two points about the document?

DR. SOLOMON: Uh-huh.

DR. SCHIFFMAN: One it says should "...result in adequate power to detect a difference between the two methods," page 12 at the top. Now, the two methods being what? Am I in the right--

DR. SOLOMON: Where are you on page 12?

CHAIRMAN EGLINTON: Right at the very top. The first line.

DR. SCHIFFMAN: I see this as the perfect application of sort of an expert program, in which an expert

colposcopist is used to train a machine and then is compared against local on-site colposcopy. So I see sometimes this as the two methods being colposcopy and the machine. I was expecting it to be a design where it was just an ASCUS Pap smear is then scanned with the machine and then taken to colposcopy and the two results are compared and then somehow adjudicated.

But when it said here, "between the two methods," I didn't know what it was talking about.

And to finish my comment, the data analysis just says "positive predictive value"--why not negative predictive value? That is very important with triage. Those are the two.

DR. O'LEARY: Dr. Schiffman's comment would be easiest to address just by taking that first sentence on page 12 and terminating it after the word "power" because there could be a variety of study designs and methods, and we are being too prescriptive. I agree with the second comment.

DR. DAVEY: So right before data analysis--I am trying to take notes here--we are going to--okay.

CHAIRMAN EGLINTON: I think we were looking at predictive values rather than just positive.

DR. DIAMOND: And depending on the device, if a

device only tells you, yes, go on to colposcopy or, no, you don't have to, that is one thing. But there may be other devices which give you an indeterminant grade; "Yes, you definitely need to go to colposcopy," or, "No, you don't have to, or the device says, "I don't know as well." And I think that indeterminant group would be important to know as well, where this extra device is not able to help triage one way or the other.

DR. DAVEY: There is also just one other thing, and it may not be a big deal, but we need to figure out how unsatisfactory exams are going to be considered for data analysis. Are we going to eliminate them or are we going to count them as negative? It goes with Paps and with the--for the prior indication or maybe some of the later ones and, also, for what like you are saying we might have indeterminant results.

So there are going to be other areas that are not just strictly positive or negative.

DR. LEVY: Okay. So in our guidance document, we just need a sentence that says the company will address a way of managing that data. We don't have to tell them how to do it.

DR. SCHIFFMAN: We've been encouraging companies to accept the fact that if a triage technique is

unsatisfactory it is a failure because a procedure has been done with no benefits.

CHAIRMAN EGLINTON: Exactly.

DR. SCHIFFMAN: So we have been including them as--

CHAIRMAN EGLINTON: Because they are trying to prove the benefit of adding this implement--

DR. SCHIFFMAN: A practical benefit, and it should have a very low failure rate.

DR. DAVEY: So needs to address--

CHAIRMAN EGLINTON: Technically inadequate examinations.

In both of these, and I haven't looked, is it in all four of these indications the study should include at least three clinical centers? Can somebody comment on that? Was that inserted by one of the panel members?

DR. SOLOMON: I think it's under all of them.

CHAIRMAN EGLINTON: Does whoever inserted that feel strongly about that?

DR. ROBINOWITZ: This is just sort of routine in the in vitro diagnostic area, but it was an attempt to try to get some idea of the transferability of technology from center to center. I think it's a good idea.

CHAIRMAN EGLINTON: What happens to us next then

is an argument over the ability to pool the data. First we have to prove that the data from the three centers are equivalent in order to be able to pool them.

Dr. Hirsch has approached the table at exactly the right time.

[Laughter.]

DR. HIRSCH: What I'd like to suggest is that, rather than pooling data, that we pool the information, the estimates.

The problem with pooling data is that you can get an apparent association that is not really there just because of a bias. This is called Simpson's paradox. It has nothing to do with a bloody glove, though.

[Laughter.]

DR. HIRSCH: My students like that. So I think pooling data is something that is very dangerous and not necessary. So the approach, rather, is to find out whether or not you think that the data from the various sites are estimating the same thing and, if they are, then you combine the estimates to get the additional statistical power and precision, but not just throwing all of the data in the bucket.

MS. YOUNG: Can I carry that sort of a bit further? Do you really feel that multi-center studies

cannot be trusted?

DR. HIRSCH: Oh, not at all. It is just the approach to analyzing the data from multi-center studies. The appropriate approach is to-- let's say that we have a multi-center study in which we are trying to estimate the sensitivity of a particular device. Rather than just taking all of the data that came from the various centers, the appropriate statistical approach would be to estimate the sensitivity in each of those sites and then somehow get an average of those sensitivities for greater precision.

So multi-center studies are fine. It is just you have to keep in mind all of the time you are analyzing the data that different data came from different sites.

CHAIRMAN EGLINTON: Is this in the category of medi-analysis? I mean, you are combining variances with a medi-analysis--not combining, pooling the data.

DR. HIRSCH: The general term that is given to this, I guess, is stratified analysis in which you maintain the individual strata or site-specific data, but you analyze within each site and then combine that information together.

The thing that has gotten confused is what we mean by combining information. That doesn't mean combining data. It means combining estimates.

You can really get, as a matter of fact I could

sketch out an example of Simpson's paradox on a transparency while we are talking about other things, if you would like, and then I will show you later how lumping data together can result in things that are very surprising and incorrect.

CHAIRMAN EGLINTON: I would suggest that rather there be just some mention that appropriate statistical techniques to combine estimates would be used if a study is done in more than one center.

DR. O'LEARY: I think that, perhaps, it's a good idea to specifically state that the data should not be pooled, that a stratified analysis should be done and perhaps provide a reference in this case.

In looking at the stuff that I remember seeing going through clinical laboratory devices, at least, I think that the availability of the statistical techniques is not necessarily well known in the statistical consultants that are being used by many members of the medical device community and that that will point them in the right direction.

CHAIRMAN EGLINTON: Right. Because it's been an argument for every PMA discussion that I have participated in since I've been coming here for eight years, the same argument comes up when there are multiple centers. And there are many examples in perinatal medicine where the

medi-analyses are done.

If you look at ruptured membranes and antibiotics, ruptured membranes and steroids, and so forth, there is one medical center in Florida that shall remain nameless, where there was a large difference, and if that one medical center is extracted from all of the medi-analyses, there is no difference.

DR. HIRSCH: I think that one thing that might clarify this is to draw a distinction between two phenomena that are related to combining data.

One is called effect modification. Effect modification is the sort of thing that you are referring to in that nameless Florida study, in which there doesn't seem to be a common value that the different studies or different sites are trying to estimate. There is something qualitatively different about some of the sites.

In that case, it doesn't make sense to combine the information from different sites because they are estimating different things.

The phenomenon that I was referring to that is known as Simpson's paradox is confounding. With confounding what happens is that you have an association of, say, the prevalence of disease in different areas, and you also have a different frequency of positivity in different areas. If

you look at the areas alone, you may see absolutely no distinction, no relationship with the test. But when you put the data together, suddenly because of these correlations with other things, you get an apparent association between positivity and disease status.

So that is confounding. Confounding is the reason we don't combine data, but we don't worry about it when we combine estimates. Effect modification is what we worry about when we are thinking about combining estimates, whether or not that is biologically a clinically sensible thing to do.

So the medi-analysis example is one of effect modification.

CHAIRMAN EGLINTON: Dr. Schiffman?

DR. SCHIFFMAN: Some people have trouble finding statistical advice, and I don't mind seeing simple analyses as long as the data for each site are available, as long as I can check that there is no--Simpson's paradox is a somewhat rare aberration, a marginal thing. It is not the common sight to have this worry, and I think as long as--across any important variable or stratification, the primary data should be shown. That is what I would say. After that it is just conveniences.

I don't mind pooling as long as that's homogeneity

evident in each of the strata. If each of the centers looks exactly the same, there is no weird marginals, then you combine it to show an overall effect. Nobody has been misled.

CHAIRMAN EGLINTON: I think the two issues that come up there are, No. 1, there may be large differences in different populations regardless of the outcome variable you are assessing and, No. 2, you may have a very large Type 2 error at each of your sites, and you have to answer both of those challenges.

DR. DAVEY: So what do we want to say here?

DR. HIRSCH: What Dr. Hirsch said.

[Laughter.]

CHAIRMAN EGLINTON: I mean, Dr. O'Leary said we should have some reference, some specific reference to appropriate statistical techniques.

Ms. Domecus?

MS. DOMECUS: FDA's guidelines on PMAs state that they will accept data from single-center studies, but you have to provide justification as to why that data is representative of the population as a whole. So I am wondering if we can't be more flexible here, and instead of saying it has to be at least three centers, just be consistent with the PMA guidelines and say, if only a

single-center study is done, you have to provide a justification.

CHAIRMAN EGLINTON: Yes. We wouldn't want to promulgate a guideline that violates FDA regulations.

MR. DOMECUS: It is not a regulation. It's another guideline, but--

CHAIRMAN EGLINTON: It's just a guideline you said? It's not part of the federal title.

MS. DOMECUS: No. It's the PMA guideline.

MR. POLLARD: Yes. I would agree that is the conventional, general, across-the-board guidance FDA gives manufacturers; the concept being that people wonder whether what you are seeing is just a simple center effect and whether it could be applied across-the-board. It is written in the most general way so as not to tie anybody's hands when you don't even know what device they are talking about. That is very general.

You could leave it like that, but that is basically giving no guidance at all to the manufacturer in terms of whether or not multiple sites have preferable and maybe even anticipating some of the likely kinds of effects you would see, so that you might put in the appropriate statistical reference for handling that.

So that is a panel comment. The whole guidance

document is, in fact, just that--guidance.

MS. DOMECUS: It's probably a moot point anyhow, given the numbers of patients we are talking about.

DR. O'LEARY: I think leaving in the reference to three or more is a good idea. It is not a lithotripsy machine we are looking at. I think you would have a hard time convincing a panel with a single-center study, and I would hate to offer much encouragement to a manufacturer to come in with one just because then they could invest a lot of effort just to find a skeptical panel at PMA time.

DR. SCHULTZ: I think that i sa good point. I think, basically, what we are looking at here is multi-site studies. I don't think you necessarily have to specify the number of sites, but I think that one of the reasons that we don't specifically say you have to do more than one study is because normally for these kinds of products we would expect to see a good multi-site study with appropriate statistical analysis and just leave it at that.

DR. DAVEY: Can I just ask, for this data analysis, I have written down the positive predictive value and negative predictive value of the ability of the in vivo detection device to identify patients with all SIL-plus lesions or HSIL-plus lesions should be calculated. Is that reasonable? So we are doing it both all SIL-plus and then

HSIL plus, and I have taken out "as determined by directed biopsy" since that may vary depending on the triage thing. I have taken out the ASCUS/LoSIL.

DR. SOLOMON: I don't know if we want to get this detailed, but I would think for LEEP we really would want to restrict it to HSIL. But that may be too detailed.

DR. LEVY: I think that's too detailed and I think that's dictating clinical practice because, as we heard this morning, there are places where people are recommending LEEP for low-grade SIL. So I would just leave it out.

DR. DAVEY: But that's all right otherwise? I've got the LoSIL plus, and I've got the HiSIL plus, and I've taken out some of the specifics because there is actually a missing parenthesis somewhere the way it is now.

CHAIRMAN EGLINTON: What do you mean when you say LoSIL plus?

DR. DAVEY: I mean everything--to detect anything from LoSIL on up--LoSIL, HiSIL, cancer--or SIL NOS is, you know, and then HSIL would be HSIL and cancer, HSIL plus.

CHAIRMAN EGLINTON: We have talked about indications inclusion/exclusion. We have talked about reference diagnosis and this level for triage reference diagnosis. We have talked about having some sort of single referee site where everything is adjudicated up front.

DR. DAVEY: Yes, and then I guess are we going to consider the colposcopy exam? We sort of talked a little bit about that. I don't know if we came to any conclusion other than the appearance needs to be considered along with the--colposcopy exam needs to be considered in conjunction with a biopsy diagnosis, but I don't know exactly how we specifically handle that. Do we just leave that up to the study design or what?

DR. DIAMOND: One way to handle it potentially for the companies would be to have cervicography and to have both the photographs and the slides available for the outside reviewer. And I would think, also, the outside reviewer, although we talked about peers, is actually applicable for our first indication we talked about before lunch as well.

CHAIRMAN EGLINTON: And we have already talked about sequence of testing. That would not really change for Indication 1 or Indication 2. Feasibility versus efficacy, in terms of study design, doesn't really apply any more once we have gone beyond Indication 1. Is there anything else anyone wants to say about Indication 2, triage?

[No response.]

CHAIRMAN EGLINTON: How about Intended Use 3, Localization?

DR. SCHIFFMAN: I have a--

CHAIRMAN EGLINTON: Dr. Schiffman?

DR. SCHIFFMAN: Record keeping for the two-dimensional cervix requiring either grid systems or marked digitized colpo photographs, I mean, coming off the digitized--is really complicated to make into records and to data sets. And, also, there are a lot of assumptions in terms of agreement, not agreement, that have to be made in terms of millimeters apart and also the location of what is a critical distance and how you adjudicate that is very tough.

I don't know how to recommend caution, but this is a field that has very few people working in it in terms of the actual statistics of this. A group in NIH is working on that with Diane Solomon. They should seek consult early in developing their data collection instruments, otherwise you will get topographic data that just will be very messy to look at.

DR. O'LEARY: I don't understand enough to comment on the study design of a lot of those sorts of issues. But I think someplace here, if possible and reasonable, consideration might be given to a comment that devices brought in for Intended Use 3 may be subject to restricted marketing.

Taking out 3 and then watching the marketing go out, establishing it for Use 3 and then watching the marketing go out in off-label use for Intended Uses 1, 2, and 4 worries me a lot more than watching it go off-label for other reasons.

CHAIRMAN EGLINTON: That is certainly going to apply or be a risk anyway, a hazard, for a company that offers a PMA with specific intended use. It may very well be restricted just to that use, which is appropriate.

DR. DAVEY: In relation to Dr. Schiffman's statement, this letter--and I don't know enough about this--but from the letter from the ASCCP, they recommended computerized digital imaging as the best documentation of biopsy site placement. Does that seem to--

DR. SCHIFFMAN: There are two companies currently operating in the U.S. that I know about. And those units, though, break down still.

They are also nifty, and so people have the tendency to want to show the patient the image, which leads to certain issues about patient follow-up, and the image darkness depends on different lighting qualities and some people have focus issues.

They are just not immediate to enter, but the software is improving, and we find them useful, but we also

find cervicography with a mark useful, and we also find the systems like the Reed--if it is the Reed-Coppleson, I don't know, system of marking on a grid with a clock face with A-B-C-D-E useful.

But there are many different methods and they have to make it very clear which one they are using and how they are going to enter it into a data base.

DR. DAVEY: So what should we suggest then? Just concerns about--

DR. SCHIFFMAN: A validated topographic measurement system that is amenable to data analysis.

CHAIRMAN EGLINTON: And as Mark said, the software in this area is changing rapidly. It is entirely conceivable that by the time somebody designs this study that miracle working software for topographic statistical and treatment will be available. Tim is shaking his head.

[Laughter.]

DR. O'LEARY: They may have it, but the analytic problem remains in terms of distancing algorithms and so forth. This is an old, old problem. It is the old "bombs in London problem" and how close was this to target, and they are arguing over that in Desert Storm and all. I think a statement to the effect that these are difficult issues and that extremely careful attention to design and data

analysis is warranted should put them on fair warning that they are going to have to really do a sell job when the PMA comes in.

CHAIRMAN EGLINTON: Can we assume, as we did for Intended Use 2, that every place necessary we can drop out terms like either ASCUS or LSIL-- clean this up a little bit?

DR. DAVEY: So they can use this for other indications, too, is that what we are saying, for the biopsy localization?

CHAIRMAN EGLINTON: Just trying to back away from too much specificity here in the language so that we are not getting involved in semantics.

DR. SOLOMON: We can use the language we had for the previous indication; an abnormal screening test result.

CHAIRMAN EGLINTON: Right.

DR. SOLOMON: Given what was said before about not dictating clinical practice, perhaps the hypothesis should be changed to the ability of the device to select the biopsy site indicating the most severe abnormality as opposed to a high-grade lesion.

DR. LEVY: I think that is good.

DR. DAVEY: So we're saying for the hypothesis, ability of the device is to select what appropriate biopsy

sites is--what is the end of it here?

MR. POLLARD: Dr. Eglinton, I think there is a suggestion almost identical to the one Diane just made in that letter from the society that says the hypothesis should be something along the lines of, "The ability of the in vivo device to select the most abnormal area for biopsy is as good as or better than colposcopy." Is that what you are--

DR. SOLOMON: Yeah. I actually prefer that wording.

DR. DAVEY: So I can just say see the letter from--

CHAIRMAN EGLINTON: Right. That is on page 3 of the faxed letter in the middle of the page. For those who don't have it, the suggested hypothesis from Dr. Cox was, on page 12, "The ability of the in vivo device to select the most abnormal area for a biopsy is as good as or better than colposcopy"--suggested hypothesis.

Further commentary on Intended Use 3? Are we happy with 3?

[No response.]

CHAIRMAN EGLINTON: Ready to move on to 4? Intended Use 4--Primary Screening Device. The device will replace the Pap smear.

DR. DAVEY: I would like to just make several

comments that we have been talking mainly about squamous lesions, and the Pap smear is not perfect for detection of other lesions, but it is better than nothing. And so if there were any thought of replacing the Pap smear, we would have to include a lot of very rare--of adenocarcinomas, glandular lesions, and unusual diseases, as well as a huge variety of patient types. I mean, it would just be a huge undertaking.

CHAIRMAN EGLINTON: Dr. O'Leary?

DR. O'LEARY: I understand the comment and whether or not I agree I am not certain because if you are able, using a new device, to reach a group, for one reason or another, effectively and treat them that you won't treat with the routine Pap smears being done now, I might be willing to let that occasional adenocarcinoma of the ovary go. I would like to be able to get the endocervicals, certainly. I would like to get everything we have right now, and I think it's a hard criterion to replace, but I think that that is within the realm of possible indications for use.

I think this is one of those things that I think we'll end up needing several, a lot of studies. I mean, because the first thing you are going to have to do is some kind of a study in which you are absolutely certain that all

of these women are going to get Pap smears in a two-armed sort of fashion or double crossover or crossover design. I am not sure what it is, and that is going to be one heck of a big study, and maybe we don't even need to worry about it. I can't imagine anybody coming in as first indication for use with this.

CHAIRMAN EGLINTON: Dr. Schiffman?

DR. SCHIFFMAN: There are pockets of inaccessibility in the United States, and then, of course, most of the world has inaccessibility to cytologists. So I would have rather this been worded as used like the Pap smear or used in some way because you would want it to be a general screener that is good enough.

What if the cost--I know you are not allowed to consider cost-effectiveness--what if it costs 20 cents? What if you can go "beep, beep, beep, beep" and you take it everywhere, in mountainous areas of the--I mean, so, I don't know. I am just saying.

DR. LEVY: Or the issue of getting an immediate result in an inaccessible population where you could treat right away if you had the confidence in the results. There are some significant patient benefits to something that wouldn't require sending out to a lab and then an answer back.

DR. SCHIFFMAN: Used a primary screening device.

DR. LEVY: Primary screening device for cervical cancer.

DR. SCHIFFMAN: Without taking a competitive--

DR. DAVEY: Yes, that would be more acceptable to me. I just wanted to bring up the point. I think somewhere we need to discuss the fact that right now we don't know enough about these in other diseases. Maybe all of the other studies will show what we need to know.

CHAIRMAN EGLINTON: Ms. Young?

Ms. YOUNG: Yes. I would just like to say that I think that the public confidence in the Pap smear is decreasing, and so just the idea of a concept of an alternative device that is faster, simpler, more cost-effective involves far fewer opportunities or steps or stages for mistakes, as appears to happen with a Pap smear, and that the public is becoming more aware of.

I think that one needs to start somewhere with perhaps looking at an alternative, and even though this might be very expensive, the studies are going to be very expensive and very complex. I don't see that as a reason not to start.

DR. O'LEARY: I think maybe the special issues for consideration, if I were going to toss it up, is just that

it's highly likely that approval of such a device will require multiple studies under multiple conditions in many different patient populations.

CHAIRMAN EGLINTON: Is there any way we could work Avogadro's number into that statement anywhere?

[Laughter.]

DR. O'LEARY: I hope it wouldn't be that many studies.

[Laughter.]

DR. SCHULTZ: The other thing is to begin with it may just require some appropriate labeling. We went through this when we have recently looked at a number of devices for treating PPH that don't necessarily allow you to sample tissue and, clearly, that is a problem when you are talking about an incidence of prostatic cancer, and some of these devices allow you to shrink the gland without actually sampling tissue, and basically we handle that in labeling by just warning people that if there is a significant risk or if that is a significant concern that this may not be the appropriate device. And for some of these things, labeling may be able to deal with some of those issues.

DR. DAVEY: So how are we--we are trying to figure out what to write down over here. Are we going to change the intended use to replace the Pap or are we going to leave

it in?

CHAIRMAN EGLINTON: We really haven't said anything that alters that significantly. I mean, Dr. Schiffman has a nice twist on the semantics, but still the point is the women who have this procedure done instead of a Pap smear have it done instead of a Pap smear, for whatever reason; they live in the Andes at 75,000 feet and no cytologist can be exposed to fumes at that elevation.

[Laughter.]

CHAIRMAN EGLINTON: Still, they don't have a Pap smear.

DR. SCHIFFMAN: Well, it's inflammatory language. It's close-the-door language.

CHAIRMAN EGLINTON: That is true.

DR. SCHIFFMAN: And I don't see why to do that. Because for a lot of wealthy places with emerging cervical screening areas--maybe wealthier than us--they are not sure if they want to go straight cytology because of the troubles with the cytotechnology recruitment and maintenance and everything. So there's going to be a lot of places looking at this, and maybe this will be something done overseas.

CHAIRMAN EGLINTON: If it's done in Guanacaste Province, could I volunteer? For those of you who don't know, the Guanacaste Coast of Costa Rica is one of the

premier surfing spots in this hemisphere.

[Laughter.]

DR. SCHIFFMAN: I prefer people to have the impression you do of people disappearing into primitive hills.

Actually, our response rate is 93 percent over three years. So our follow-up is better and the people are universally literate. But if you want to think it's bad, I'm going in two weeks. I'm looking forward to it.

[Laughter.]

CHAIRMAN EGLINTON: Take your sunscreen.

MS. YOUNG: Can I suggest, perhaps, replacing the word "replace" with "used as an alternative to" and then that wouldn't completely sort of wipe out the Pap.

DR. O'LEARY: Can I suggest that Point 2 be reworded then, that the study must establish a high degree of confidence for the sensitivity and specificity diagnosis?

DR. DAVEY: Where is this?

DR. O'LEARY: Under special issues for consideration. That just to say that the study must establish a high degree of confidence for sensitivity and specificity because, in fact, it's conceivable that one could knowingly approve a device that has half or less the sensitivity. As long as that is an established indication

for use, that seems to me to be within the realm of possibility.

CHAIRMAN EGLINTON: Is there any further comment on Intended Use 4? Dr. Davey is--

DR. DAVEY: We are trying to figure out, too, about the ASCUS.

DR. SCHIFFMAN: Just delete ASCUS.

CHAIRMAN EGLINTON: Measure of truth.

DR. LEVY: Why don't we say, "The measure of truth will be colposcopy on all abnormal results," and that way we are saying for the device abnormal results they get colposcopy and for Pap abnormal results, whatever that abnormality is, they get colposcopy, and then we are being clean about it.

DR. DIAMOND: I'm not sure why this design would have to include a Pap smear. If everyone would get the device and then get colposcopy, that would probably be another alternative.

DR. SOLOMON: I share concern about closing the door to new technologies coming to replace the Pap smear, but I also wouldn't want to hold out false hope for a company who is going to come forward with a trial to be an alternative to Pap smears and have a panel actually consider an indicated use of this to be a substitute for Pap smear

screening.

The likelihood that a panel would accept that without a comparison of cytology, which is the current standard, I think is very, very small. So, while I share the concern that we shouldn't be too restrictive, I don't think that we should offer false hope either.

DR. O'LEARY: Maybe a way of handling that would be, again, someplace or another a comment to the effect that, in the event that a company would come forward with this as an indication for use but not as an alternative for Pap screening, it is, first of all, this is likely to be viewed--is likely to receive a high degree of scrutiny by the FDA and would also, in all likelihood, require all documentation to include a statement to the effect that this device is not intended as a replacement for the Pap smear.

I think, first of all, that would likely be a requirement that would be put on or recommended by panel. And I think the high degree of scrutiny, once one has stated that, ought to put people on warning that this is likely to be a high hurdle to jump over, and this transcript is publicly available.

DR. DIAMOND: But that is not the intent of this Intended Use No. 4. Intended Use No. 4 is specifically as a primary screening device. That is what we are now

discussing. I will defer to others, but I thought that colposcopy is the gold standard compared to the Pap smear. We don't do colposcopy on everybody because of the cost and the time associated with it, but that if we could, we would love to do that.

So if you have that as the standard, I don't know that you need the Pap smear.

CHAIRMAN EGLINTON: I think Dr. Solomon's point is powerful. Yes, there is a large public outcry--no, a small public outcry in response to a large hysteria outcry among the lay media over Pap smear issues, but I think it is going to be real hard to take Pap smears away from the American public. That is going to be a tough sell.

And the panel members are part of the American public. I don't think anybody is going to be able to offer easily a protocol that purports to satisfy all of the arguments that are going to come up if somebody says this tool is going to be a good substitute for a Pap smear.

DR. LEVY: Michael, there's another issue with respect to cytology, and that is that colposcopy may not pick up glandular lesions. You can't see up there. You will have inadequate colposcopies. So I think that including cytology and Pap smear for this particular indication makes good sense.

DR. DIAMOND: Again, it depends what you do at the time of your colposcopy. If you do an ECC, you will be able to glandular tissue and be able to assess that. It depends on how you design the entire study.

DR. SOLOMON: Pathologists who have read a lot of ECCs know their very limited value.

DR. LEVY: And, actually, there are some papers now showing cytobrush is better than ECC for picking up lesions in the canals.

DR. DIAMOND: We could use cytobrushes as part of the colposcopy.

[Laughter.]

DR. DAVEY: Well, the colposcopy, too. Don't we think we have to, in this indication, do colposcopy on a portion of the negative patients by device, too, because--

DR. DIAMOND: All of them.

DR. DAVEY: I thought I heard colposcopy on any abnormal result, or are we saying colposcopy on every patient? I have heard a couple of different things. I am trying to figure what--

DR. LEVY: It says right now colposcopy on a portion of the negatives, and I think we should leave it open for the companies to elect a study design that is reasonable for them.

DR. DAVEY: Okay. So, "Measure of truth will be colposcopy on all abnormal results and at least a portion of negatives," right?

CHAIRMAN EGLINTON: I would be willing to--I shouldn't say that--I'll guess that nobody is going to come forward with a PMA for this intended use until there is more experience with this. There have been some other uses. It's been in the marketplace. It's been used, and then somebody says, "Gosh, this really is the best thing since night baseball. Let's go forward and test this as a primary screening tool."

DR. O'LEARY: The other thing is I think a lot of the details are really handled to establish a high degree of confidence for sensitivity and specificity because a high degree of confidence, in this case for the predictive value of a negative result, is going to require them to do--they are going to have to compare it with cytology with colposcopy and with divining with a crystal ball, I think.

[Laughter.]

DR. DAVEY: Yeah, you almost think that we may need to readdress this. We can think of some things now, but I am not sure if we can come up with everything right now on this. I sort of hate to try to spend a lot of time, but then you don't want to say it is finished either by not

spending as much time talking about it now. We don't want to act like we have all of the answers.

CHAIRMAN EGLINTON: I think Dr. O'Leary's point was these transcripts are in the public domain. You can buy the videotape. I think you can get a sense that this is not going to be easy if you think you are going to get labeling for this as a primary screening tool. It is going to be a difficult row to hoe.

Does anybody want to see anything more specific on this Intended Use 4?

[No response.]

CHAIRMAN EGLINTON: I think we have finished 3, talking point 3. Colin, do you think we finished talking point 3, "Effectiveness"?

MR. POLLARD: Yes.

CHAIRMAN EGLINTON: We are ready to move to talking point 4? I think so.

We have 4. "These may offer additional benefits..." Or they may lose some additional benefits.

DR. DAVEY: Well, one thing, if the device could be used repeatedly without altering the tissue, that is one of the things. And one of the things that we were talking about, too, is just the precision of the device. We would need to--this sort of gets into maybe Question 5, but we

need to consider how reproducible a device is in a patient and between readers. But there are advantages for the pa--a patient could probably be tested repeatedly without change to the histology and so forth.

MR. POLLARD: That was one scenario that we were thinking about that stimulated this question. Another scenario I think Barbara mentioned earlier was you have the benefit of relatively instantaneous read-out. If you have a patient group that you know the likelihood of you getting her back is very limited, how will that affect acceptability of sensitivity and specificity?

DR. O'LEARY: Can I ask a question, I guess, of the Agency on this?

If one came in with an indication for use that would try to define a population like that, do you think that can be effectively defined into the indications for use in this case--a transient population difficult to follow--or is this holding out a benefit that is difficult to define and that we know will invite immediate off-label use?

DR. LEVY: What I really think this question is asking us to do is formulate some opinions without having any data in front of us and without really knowing. I mean there are just too many hypothetical at least for me to start to answer 4 and 5 at this point in time.

So the answer to the question is that, yes, these factors will probably influence our evaluation, but without knowing what the factors are, I can't say with any reliability how that would affect my judgment on a PMA.

So perhaps the best advice we can give to companies is that common sense reigns, and we try to exercise common sense, in addition to good science, while we are here.

CHAIRMAN EGLINTON: Dr. Schiffman?

DR. SCHIFFMAN: Instantaneous readout is a massive advantage for international work. Anyone who has organized an international-type vertical program in which you come in with a van, and you want to do good, and you want to make sweeps, this is a tremendous advantage and would weigh against a lot of other misses.

So this will be a reason for the use of these products in a lot of places, and then you guys can look at the data.

DR. DIAMOND: Can I just ask you question, though? As part of your international team, if you had a cytopathologist with you, could you not take the Pap smear and look at it two minutes later?

DR. SCHIFFMAN: These are mobile van-type units with nurse clinicians, and the making of the Pap smear and

stabilizing that with reagents and making sure that everything is--it just isn't done.

DR. LEVY: Mark, could you treat them while you are there with an instantaneous result?

DR. SCHIFFMAN: Well, that would be the sort of--

DR. LEVY: That would obviously be the--

DR. SCHIFFMAN: And you would do a great deal of good in a place, like I lived in Africa, and that would be a very--

DR. LEVY: But not only in Africa. I mean, you do a great deal of good in the middle of Tacoma, Washington.

DR. SCHIFFMAN: Well, I know, but you were saying we can't estimate that kind of an effect here in the U.S.

DR. O'LEARY: Question to the Agency on international because it's a place where I don't know where the statutory--

If a device is manufactured in the United States for export only and not used in the United States, does the Agency have jurisdiction over that manufacture and sale? Do we care?

MR. POLLARD: The rule of thumb there, and I am not an expert on this, we have a group in our Office of Compliance that deals with that kind of issue, is, essentially, that if FDA doesn't know of a known risk for

that device, that it causes some kind of very quantifiable injury and the country of import acknowledges that it is acceptable to go there, then that is perfectly okay.

DR. SCHULTZ: I would just like to comment. It sounds like we are treading on some very thin ground here, and there are a lot of very good questions here that we probably are not going to be able to answer definitively.

My sort of gut feeling is that I am not sure that in order for a device to get on the market as a screening device that it has to, in all of its various manifestations, be as good or better than Pap smear and that there may be certain conditions where a device could demonstrate clinical utility as an alternative, as has been said, not necessarily--I think alternative is probably a better word than replacement--but as an alternative, and that some of these questions that are being asked about defining populations and things like that, while difficult, I guess I would not like to say are insurmountable, and that if a device, for instance, were able to demonstrate a certain sensitivity, specificity that were not completely off the wall with respect to Pap, that we might be able to say as a group, both Agency and advisory panel, that we see enough clinical benefit because of these other factors, that that device should be allowed on the market.

So, again, I think that, while I don't have a definitive answer, I think that, probably for the sake of this kind of document, what we probably don't want to do at this point is be so specific that we preclude a lot of intelligent people in industry from trying to pursue something that could be doing a lot of women a lot of good and that we would certainly try to take a broader view of these things when they come in.

CHAIRMAN EGLINTON: So we don't want to get very specific on this Item 4. Colin, is that okay?

MR. POLLARD: Yes.

DR. SOLOMON: I was just going to suggest that what we might want to do is to bring in the concept that an immediate readout would be a tremendous advantage, just include that in under No. 4 to balance out both what would have to be done, but also the benefits that might be yielded.

CHAIRMAN EGLINTON: Before we go on to 5, can we look at the other points. The last page of our agenda--Colin, are you looking at this, also?

This is the last page of the agenda, the annotated agenda. I guess this would be more useful if more people could look at it and decide whether we covered these things or not.

There is another three-quarters-of-a-page of just discussion.

MR. POLLARD: There were a number of just sort of minor points that some of the reviewers had sort of compiled and just kind of wanted to be sure as the panel went through.

CHAIRMAN EGLINTON: Dr. Harvey has copies. Could we just pass them around at least to the members of the panel here so we can see that we have covered these things.

The first topic was, "Do other optical diagnostic technologies that expose mucosal surfaces to light; e.g., colposcopy, laparoscopy, approach or exceed the previously mentioned standards? Are they appropriate standards?

I think Dr. Richards-Kortum mentioned that there is a lot of wattage that is reaching the surface of mucosal organs in endoscopy.

DR. RICHARDS-KORTUM: Yes, especially endoscopies where they are used the 1,000 watt mercury lamps.

DR. O'LEARY: Also, gingival surgery and some other places, there a number of--mainly cutting, but they are certainly exposed.

MR. POLLARD: Gary, my own impression in looking at that is, just in general, we have pretty much covered everything under those points. I am just looking at those--

CHAIRMAN EGLINTON: I think we have pretty well covered all of this. We didn't talk really about inflammatory conditions of the cervix. Current practice when performing a Pap smear calls for caution, invasive, infectious, or inflammatory cervical conditions. The same cautions apply to this new technology."

Does that say anything to anyone?

DR. DAVEY: I thought when we discussed some of the feasibility studies, that we just don't know enough about this, and so I had kind of written down that this needs to be considered by the manufacturers.

CHAIRMAN EGLINTON: At the feasibility level.

DR. DAVEY: Yeah.

DR. O'LEARY: And it will come naturally in the course of doing the studies. I mean, if we look at the Pap smears, as we do, the number of inflammatory, and reactive conditions, and infections in some populations so far exceeds the amount of SIL that the information is going to come and it just needs to be analyzed.

DR. SOLOMON: I keep coming back to page 9, that top section. Perhaps we can just add a bullet there of inflammatory/infectious conditions. It is basically a thought-provoking discussion there that this is what companies should consider.

DR. DAVEY: Yeah, I had the same thought, too, earlier about things. Some of the things, the timing of the cycle, other things bleeding, concurrent bleeding, polyps, a lot of other things.

DR. SOLOMON: Why don't we just look at this list then and see what else needs to be added other than inflammation and infectious conditions, which we have just added.

CHAIRMAN EGLINTON: It is on page 9 of the draft at the top.

DR. DAVEY: So we can say other--well, we have menstruating, but it may just be bleeding.

CHAIRMAN EGLINTON: Other bleeding.

DR. DAVEY: And then other gynecologic conditions such as polyps. There are probably others.

DR. LEVY: Cysts.

DR. DAVEY: Cysts.

DR. O'LEARY: Why don't you say including, but not limited to, and then--

DR. DAVEY: Other.

DR. LEVY: And then place inflammatory conditions as a separate bullet.

DR. KATZ: And that section there under menstruating and nonmenstruating, do we want to add

something about cycle phase? Would that be the place to do it?

CHAIRMAN EGLINTON: Menstrual day, cycle day.

DR. KATZ: Cycle phase.

DR. DIAMOND: Well, the issue is probably hormonal environment as opposed to just cycle day because you may have people on G&R genologs [ph], you have menopausal women, and so you could have very many different hormonal environments.

CHAIRMAN EGLINTON: So each of these patients should have an LHFSH prolactin, estradiol, and P-4 drawn on the date of--

[Laughter.]

CHAIRMAN EGLINTON: Could we at the prodding of an FDA panel member on my left, could we please turn to page 2 of the draft and look at each section here. And looking at 2 through--a lot of this we have already discussed building up--but look at pages 2 through 7 1/2, up to the top half of 8, to see is there anything else that we need to insert or edit?

MS. DOMECUS: I had a question. The requirement that these devices be sterile, I have been informed by one of the manufacturers that that is inconsistent with the requirements for speculum, cervical brushes, and sticks. So

I think the FDA just needs to look into the inconsistency or if there is a reason for that or not.

CHAIRMAN EGLINTON: That is going to be a very hot topic if somebody proposes to put something on the cervix and then re-use it with another patient. Professor Coppleson talked about the sheath arrangement that they are developing or have developed. I think it's imperative that, if this is actually going to come in contact with tissue and that it is going to be re-used, it has to have some sort of sheathing and/or sterilization between patient use/treatment.

DR. LEVY: I think there are two issues there; one is protecting the patient from transmission of disease, and the second issue was is it necessary to have a sterile device in order to sample anything on the cervix, and the answer to the second issue is, no, it certainly doesn't have to be sterile, but the answer to the first is most definitely we have to protect patients from transmission patient-to-patient. So there are two issues there.

CHAIRMAN EGLINTON: And that will be the issue that shoots it down if they can't satisfy the fear that a disease might be transmitted from one patient to another.

DR. NEUMANN: Dr. Eglinton, I do have a couple of issues that, perhaps, are in this statement on page 2, but

not emphasized enough.

One is referring to the model. I think whatever model means--I don't really know that--but I think what we certainly would want to know is the underlying physiologic principles involved in the device and to make sure that the studies done are appropriate for that.

The second issue, I think, is with respect to actually visualizing or, in the case of devices that contact the cervix, contacting the cervix, and I think in either case it would be important for the manufacturer to demonstrate that there are not areas of the cervix that are inaccessible to the device, either due to the positioning of the cervix and the uterus or due to, perhaps, the anatomy of the patient in profoundly obese patients and things like that.

I think that, as someone mentioned a few minutes ago, the reproducibility of especially those devices that have to be aimed to a particular point, the reproducibility of an operator to be able to do that in a consistent way is also important.

DR. O'LEARY: Isn't the business of the location pretty much handled under principles of operation? I mean, I am presuming that the high e end of the endocervical canal is going to be inaccessible to most of these devices, and I

am much more concerned that they define exactly what it is they can see and can't see rather than ask that the entire cervix be accessible. I think it might be reasonable to ask that the transformation zone be accessible.

And even there we have to define that probably they should state as to whether the percentage of women in which it is accessible, you know, something in the way of defining the result. If it is only accessible in 10 percent, then as long as they label it that way--they'll have a hard time selling it, but--

CHAIRMAN EGLINTON: So is page 2--any further suggestions on page 2 or page 3?

Ms. Young?

MS. YOUNG: I am not sure if this is the appropriate place, and I can't remember now whether it is somewhere else, so I better mention it while I am thinking of it. Concerning operator training, is the manufacturer required to give some guidance in terms of training for a new device?

CHAIRMAN EGLINTON: Yes. There is some, there is a sentence on that topic on page 9. It may not be strong enough, but there is a sentence on that topic.

MS. YOUNG: It's just that when I think of one of the problems that is, perhaps, becoming more widely known

about the Pap test is that the actual operator--at the beginning, the individual who actually performs the test sometimes or maybe always or perhaps for years, and years, and years hasn't done it with the appropriate skillful technique, and that may be something that one might never know, in fact.

CHAIRMAN EGLINTON: Any further comment on that, since we are talking about education?

DR. RICHARDS-KORTUM: Along with training issues, I think that the guidance document should speak to calibration of the optical devices and how we know that the sensitivity has been calibrated properly for wavelength-dependent variations.

CHAIRMAN EGLINTON: I am looking to see if there is something on that on page 3 or 4. It looks like it might be. That should be somewhere in the operation of the equipment is something about calibration requirements.

DR. O'LEARY: Max, are there some documents for clinical laboratory devices, guidance documents, that could be used to address the calibration issues here? Because there has been a lot out on self-calibrate, both self- and external calibration that we dealt with over there, and I wonder if they can't cross-reference to use.

DR. ROBINOWITZ: Well, I think, also, maybe, as

Dr. Katz pointed out, about use of phantoms. Perhaps we can get from several areas some information.

CHAIRMAN EGLINTON: I don't see that in here anywhere, but obviously something along the lines of performance standards, calibration, ongoing performance standards, phantom imaging, that sort of thing has to occur somewhere, it has to appear somewhere in here--under device performance, perhaps, laser optical issues, somewhere.

DR. O'LEARY: And, also, electrical issues for those things which may be using electrical stimulation.

CHAIRMAN EGLINTON: Yes, somewhere under device performance a lot of that technical work has to be--

Anything else on page 4? We have actually spent a fair amount of time talking about these issues.

DR. DAVEY: How much are these--these devices wouldn't be covered by CLIA regulations, correct?

CHAIRMAN EGLINTON: CLIA regulation applied to this sort of device? I don't think so.

DR. DAVEY: They would not apply to this, right. So there are some other regulations that would apply, I am assuming, but I don't know about those.

DR. ROBINOWITZ: I don't think the Clinical Laboratory Improvement Act would cover these devices.

CHAIRMAN EGLINTON: Anything on page 5?

DR. ROBINOWITZ: And as Colin pointed out, it is not a clinical laboratory device, in vitro device.

CHAIRMAN EGLINTON: Anything on page 5?

DR. O'LEARY: I was going to say the other place that there ought to be adaptable census of regulations is some of the stuff out of the radiology side of things, ultrasound calibrations and things like that. There should be some adaptations and cross-references for general principles.

CHAIRMAN EGLINTON: Colin has that covered.

DR. SCHULTZ: It's all in our division, so we can get that information very easily.

CHAIRMAN EGLINTON: On labeling, there is not too much we can say about labeling yet. We don't have a device.

The information we talked about or the concern we expressed about contacting a patient and no patient-to-patient contamination is in here, and I guess the issue would be it must be sterilized between uses. That is not really the issue. It is not sterilized, it is just that it is not going to transmit transmissible diseases.

Can we cross out or put parenthesis around sterilized so that the meaning is really different or cross out sterilized? Decontaminated between--

DR. DAVEY: Or disinfect.

CHAIRMAN EGLINTON: Disinfected, whatever the appropriate term is that is used in--is disinfected the right term?

DR. DAVEY: Yes.

CHAIRMAN EGLINTON: And a disposable sheath may not be enough. Current recommendations for endovaginal sonography require both the use of a sheath and then disinfection after removal of the sheath. I mean, this is serious business.

DR. DAVEY: It shouldn't be "or."

CHAIRMAN EGLINTON: It shouldn't be "or."

DR. LEVY: And then we're going to want some documentation that the disinfectant solution doesn't affect the performance of the device in any way.

CHAIRMAN EGLINTON: The same way in the next paragraph, "Single-use components," disinfection.

Anything else on page 6?

[No response.]

CHAIRMAN EGLINTON: Page 7?

MS. DOMECUS: I have one minor editorial clarification. The last bullet point says "If the device is patient-contacting, do the following," and I am assuming all of the devices are patient contacting. I think what it is referring to here is that it contacts the cervix.

CHAIRMAN EGLINTON: What page are you on? I am sorry.

MS. DOMECUS: 7. I am sure what we mean here is if it contacts the cervix, not if it is patient-contacting. Aren't all of these devices patient contacting?

MR. POLLARD: I think our view on this was we could not be sure that it would actually be required to touch the cervix. So this was addressed to devices that you actually have to, essentially, drag across the cervix or we considered that there may be devices that don't even actually have to do that.

DR. LEVY: There may be devices that are aimed through a colposcope and don't contact the patient at all.

CHAIRMAN EGLINTON: It may remain four inches away from the cervix and take a picture of it.

MS. DOMECUS: And not touch the patient any other place.

CHAIRMAN EGLINTON: Maybe.

At the bottom of page 7 under "Sample Clinical Study Plan" we do have stratification here or categories. You have ASCUS and low grade and high grade. In the sense that this is offered here, is this acceptable to leave this terminology in?

DR. O'LEARY: I think it's okay. It's clearly

labeled as a sample, as a feasibility study, and the idea is just to get people to think.

CHAIRMAN EGLINTON: Dr. Hirsch?

DR. HIRSCH: One thing that might be clarified is the fact that this 100 isn't what is being advised for all applications. So maybe adding a sentence by saying, "In this particular study, the appropriate sample size required was 100" or something of that sort.

CHAIRMAN EGLINTON: Just in the sense that this, for example, here is a sample that might be tried. "Study 100 patients..." but there is nothing magic about 100 patients or 25 in each of these categories. This is one potential sample.

And continuing over to the top of page 8, or just continuing with this example clinical study.

DR. DAVEY: I thought we were going to suggest colposcopy.

CHAIRMAN EGLINTON: It's just a sample plan.

DR. DAVEY: Yeah, but we were going to suggest multiple orders of tests of the feasibility, right, to see which one was best.

CHAIRMAN EGLINTON: Right. Yes, in feasibility there also should be some studies of varying the order of events.

DR. DAVEY: Right.

MS. YOUNG: Can I have some clarification again on the issue of patient contacting, a device which is patient contacting.

Some of these devices do not actually contact the cervix, but they certainly are patient contacting. I mean, some of them apparently are inserted into the vagina, but they may not touch the cervix. Now, are they patient-contacting devices?

DR. LEVY: Yes. When I was talking about nonpatient contacting, those are some things that are aimed from a device that is completely outside of the patient from what is called a colposcope.

MS. YOUNG: Thank you.

CHAIRMAN EGLINTON: Dr. Hirsch?

DR. HIRSCH: This sample protocol in bullet 3 on page 8 I believe that what is being suggested there is the resolution of discrepant results. You are biopsying either only colposcopy positive or device positive lesions.

CHAIRMAN EGLINTON: Are you on the top half of the page or down--

DR. HIRSCH: Yes, the top. The third large paragraph with the--

CHAIRMAN EGLINTON: Right. It starts, "Directed

cervical biopsy should be done..." that paragraph?

DR. HIRSCH: Yes. It ends in, "This will ensure that sites that may be identified by the device, but not by colposcopy, are captured for histologic confirmations."

Now, even though that is resolution discrepancy, I don't know how--what you are doing is you are locating biopsy sites, and I don't know, you can't--well, I guess, the alternative would be random biopsy.

So I am not sure what to do about that, but that was just a characteristic of the sample protocol.

DR. O'LEARY: I think maybe one of the problems here is that we should be saying feasibility studies because in many cases what we are going to be looking at is somewhat different studies of different sample sizes, so like a question of ordering. And it's hard for me to imagine trying to come up with a single study to sort of answer all of these questions.

Now maybe if we say feasibility studies and then back off in calling it among the things which would be studied are--

CHAIRMAN EGLINTON: Yes, ma'am?

DR. RICHARDS-KORTUM: I think another important issue for the feasibility studies is to take a careful look at the effective acetic acid on the optical properties. We

know it has a huge effect on the phase function, and the strength, and the time following the application can potentially play a big role, and that would be important to know up front.

CHAIRMAN EGLINTON: Right. And that is along the lines of varying the order of the events or the devices used first or the Pap smear, whether the cytobrush is used at the time or the spatula or later because it causes bleeding so much of the time and so forth.

DR. DAVEY: And then, also, we sort of mentioned this, too, or maybe it is worth saying that this is where we need to consider patients for inclusion or exclusion, as we talked about earlier, is in this feasibility study is if they are going to, you know, if you are going to include a certain type of patient, then you need to test it here and make sure that it is going to be appropriate.

So it kind of goes to that page 9, where we were talking about study subject selection. But that factor needs to be included in the feasibility.

CHAIRMAN EGLINTON: It will first be necessary to demonstrate feasibility before designing the safety and effectiveness study.

DR. DAVEY: Yes.

CHAIRMAN EGLINTON: But we're certainly not trying

here today to think of all of the potentially good ideas for multiple feasibility studies, and there may be lots of ideas that people come up with.

Anything else on feasibility studies?

[No response.]

CHAIRMAN EGLINTON: Does anyone else have anything else that we have not covered on the document itself?

DR. DIAMOND: One just brief thing and that is I don't think any place have we talked about DES or DES-exposure and effects on the cervix. That ought to be something that would be, at some point, discussed, as to whether that requires any differences from anything else that has been described for the use of the devices.

DR. DAVEY: Is that going to be under study subject selection?

DR. DIAMOND: Yes.

DR. DAVEY: Can we put it as a separate bullet or under other Gyn conditions I am putting polyps. DES exposure, can I put it there?

DR. DIAMOND: Yes.

CHAIRMAN EGLINTON: Dr. Solomon, did you have anything else?

DR. SOLOMON: No.

CHAIRMAN EGLINTON: Dr. Davey? Dr. Katz? Dr.

O'Leary?

[No response.]

CHAIRMAN EGLINTON: There are several people in the audience who wanted to make other comments. Can we invite their comments, please? Yes, sir, please? Dr. Hirshorn?

DR. HIRSHORN: I am Dr. Hirshorn from Polartechnics.

I must say I feel like the guy on Friday afternoon who says, "Let's do more work."

[Laughter.]

CHAIRMAN EGLINTON: That is by design.

[Laughter.]

DR. HIRSHORN: Nevertheless, it needs to be done.

I want to clarify a couple of points that I wasn't sure of and add one or two more. The first point that was raised about the need for sterilization, even if there was a sheath, I think that that very much depends on the design of the sheath.

So, personally, I would suggest that in the guidelines there wasn't a compulsory requirement for sterilization of the device with a single-use sheath because some designs of sheaths could be full-proof. So I think it would be sheath-dependent.

CHAIRMAN EGLINTON: Right. But the manufacturer would then have to convince the panel members that there is no possibility of contaminating the device in removing the sheath.

DR. HIRSHORN: Absolutely right.

CHAIRMAN EGLINTON: That is going to be a tough sell.

DR. HIRSHORN: Yes. The sheath could be completely different design than a condom or ultrasound probe sheath.

The second point to clarify, in regard to the question of reference diagnosis, there was comment earlier in the afternoon regarding the combined evaluation of biopsies and the addition of cervicography possibly for consideration in evaluation of biopsies.

My understanding was that the panel was recommending that the colposcopy and biopsy be both taken into consideration, and in my mind I understood that that would mean the colposcopic impression itself and not simply cervicography, which is lesser because it is a static and nonlive image. I just want to clarify that that was the recommendation of the panel; that it was colposcopic impression plus biopsy, not biopsy with cervicography.

DR. DIAMOND: If you do that, you are not going to

be able to have a third party view it at later date.

DR. HIRSHORN: Well, you can also take into account digitized colposcopy, but not solely cervicography plus biopsy.

DR. DIAMOND: Yes, some form of image for another party is what I had in mind when I made that comment.

DR. HIRSHORN: As well as the written description of the colposcopic impression, perhaps the opinion of the colposcopist himself.

DR. DIAMOND: I guess that would depend on your design because that would then introduce--then you are going to have variation depending on the physician that is doing the exam, and you may want to avoid that and have just a single or a limited number of evaluators.

DR. HIRSHORN: So it depends on the study design that would allow for that.

A third point, I was very glad to see the discussion shift from statements to say that in Indication 4 that the device would not be intended to replace the Pap smear. I think it really very much depends on what the results were, given that it is a momentous type of thing you would be trying to do and 50 years of history, and that there is an intention that, ultimately, these devices will be used for primary screening.

Dr. O'Leary, there is before the FDA at the moment a protocol designed for standalone study using these devices for a standalone screening to follow the other devices. So it is not so far off. And we've had to design such tentative studies, and it is very useful to have the guidelines.

The other point regarding such studies and the studies for adjunct, in other words, studies where you combine the use of Pap smear and in vivo device for screening, in those cases, the population would be the same or at least overlap. In other words, you are looking at a screening population to be used for Pap plus device or for device alone. In that case, what I would like to hope was that the guidelines would allow for at least some aspects of the studies to be combined because the entry criteria can be similar.

Those are my four points.

CHAIRMAN EGLINTON: The first thought I have in response to that is you would have to be careful that the act of performing one procedure does not impact on the success or the predictive value of the other procedure; that you don't interfere with one by doing the other.

DR. O'LEARY: The only comment I would have is, making the assumption that the devices are very, very good,

I hope that whatever strategy you take to introduce them into the market is the strategy which works best for both getting them into the market and enabling them to be well evaluated. I have no preconceived notions, and in many ways the Pap smear is my greatest headache.

CHAIRMAN EGLINTON: Are there other comments?

Dr. Lonky?

DR. LONKY: Dr. Stewart Lonky from Trylon Corporation.

I was intrigued by the comments from the panel members and wanted some clarification that the panel was at least talking about using some other measurement in regards to Issue No. 4 or the Use Indications No. 4 regarding immediacy of results and that that was something that would be, perhaps, measurable.

And my only comment about that is immediacy itself is obviously only good if the results are meaningful.

But not to underestimate the fact that we don't have to go to Africa, you can go to a number of states in this country where you have to go out and find people, and one of the measurements would be number of interactions to correctly wind up with a correct therapeutic or diagnostic; in other words, you had asked the question about if you went out there and diagnosed it, would you treat it right then.

Either diagnosis or treatment as an outcome, if it is correct, would be weighed against the number of incorrect decisions that would be made.

It was an interesting metric, which I think the panel should think about. I had not thought of that before as something that you measure in addition to sensitivity and specificity, but there is a real advantage to being able to do a single visit and take care of what needs to be taken care of at that time, but not to be doing too much treatment, particularly if treatment is one of those arms, unnecessarily.

And then in answer to a question about immediate Pap smears, UC-Irvine has been doing what they call a Stat Pap Program for people who are very difficult to get to come back. They can do a Pap smear in three hours with relative sensitivity. So that is what they do down there. They have the women sit and wait just for information.

CHAIRMAN EGLINTON: Other comments form the audience, questions? FDA? Colin, anything else you want us to wrestle with?

Our Item No. 5, then, does the panel have any other recommendations for the draft guidance document?

[No response.]

CHAIRMAN EGLINTON: I can't believe it. Nobody

from the FDA wants to tell us anything else or ask us anything else?

Ms. Young?

MS. YOUNG: This gentleman and I just had a little side conversation, which essentially on the issue of operator education and training, but perhaps in the document that could be given greater emphasis by having a heading on that issue.

MR. POLLARD: That would be very easy for us to accommodate.

Yes, the one thing I was going to suggest, if you were thinking about getting close to wrapping up, was that we had asked Dr. Katz and Dr. Davey to maybe capsulize some of what they thought were the key panel points.

DR. DAVEY: I'm on page 11 of my notes.

CHAIRMAN EGLINTON: So we'll be back at 8:30 in the morning for that?

[Laughter.]

DR. DAVEY: Yeah. I'm on page 11 of my notes, so I think it would be--

MR. POLLARD: So that may not be a feasible approach at this point.

DR. KATZ: Just how long can you hold a crowd?

DR. DAVEY: I mean, we have come back and forth on

different points. I think it is safe to say that it is going to take several people to review our notes and to try to put it together. I don't think we can rely on one person to try to insert all of this stuff.

CHAIRMAN EGLINTON: Thank you very much for taking all of those notes, Dr. Katz and Dr. Davey, working on this. Thank you very much.

MR. POLLARD: Absolutely. We will definitely use those as we go back over everything.

DR. O'LEARY: Can I just interject one thing? It is not a comment on the document, but it is a comment, first of all, on the FDA staff. Considering how relatively few and minor the comments have been, I mean, there has been some discussion, but I think that the FDA staff did a great job in putting together both that guidance document as it exists right now and those people that helped them, and this panel meeting, and I think that you have done a great job in keeping it on track, and I think that everybody there deserves to be complimented.

CHAIRMAN EGLINTON: Thank you.

DR. YIN: You stole my line, but that is all right.

[Laughter.]

DR. YIN: From FDA, we do want to thank all of the

panel members, especially people from the in vitro diagnostic, we do thank you. And we thank the audience, also, to helping us very, very much because this document would be very, very important to us because some people may be interested in doing a product development protocol, and this will be very, very helpful.

And especially to thank Dr. Eglinton. This is not an easy panel to keep on track. Thank you so much for moving it and making it on time.

And I do thank FDA people, too. Yes, it is a good job, and Dr. Deborah Smith is not here--is she here? She has helped us tremendously from Office of Women's Health, and NIH people I cannot thank you enough that you make this document very, very good. Thanks again from FDA.

CHAIRMAN EGLINTON: Do we have a move for adjournment?

DR. LEVY: So moved.

DR. SOLOMON: Second.

CHAIRMAN EGLINTON: Thank you. We are adjourned.

[Whereupon, at 3 p.m., the proceedings were adjourned.]

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